THE OHIO JOURNAL OF SCIENCE

VOL. XXXVII SEPTEMBER, 1937 No. 5

EXAMPLES OF ORTHOGENETIC SERIES IN PLANTS AND ANIMALS

STUDIES IN DETERMINATE EVOLUTION X*

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Orthogenetic series are so prominent in both the plant and animal kingdoms that their consideration becomes of major significance in any careful study of the evolution of organisms. A few types of plant series are here presented together with several animal series in order to illustrate the nature and significance of orthogenesis. In studying living organisms one cannot tell directly, from the orthogenetic series itself, what is the real relationship of the members of a series to one another nor in what sequence they evolved; but this is after all of secondary importance. The fundamental problem is the fact that the evolutionary process brings out such a series and that these series usually have no relation either to utilitarian advantage or to any ecological conditions either physical or biological. The evolution of each series is commonly independent of other movements in the same group of organisms and may even proceed in a different direction or in a sequence exactly the opposite. In the past the most definite orthogenetic series were recognized in the fossil records and in these, of course, the direction of any given movement or sequence was definitely indicated by the succession of the rock strata in which the fossils were found.

In attempting to explain orthogenetic series in the past it was usually assumed that the series was the result of natural selection or was produced by ecological sequences, either in time or space by a direct effect of the environment. However, any one who has only a superficial knowledge of orthogenetic series and their taxonomic relations soon discovers that they

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have no general correspondence with any ecological gradations, whether considered from the standpoint of the Darwinian survival of the fittest, of a direct response to environment, or of a fancied Lamarckian use or disuse. Most of the series are found to lie entirely outside of any possible teleological implications, and have no more to do with advantageous or utilitarian determination than have the many interesting series of molecules often met with in organic chemistry or the various series of forms and patterns appearing in certain types of crystallization.

Recently certain geneticists have attempted to resurrect the natural selection corpse and to develop a new type of evolutionary theory based on the fortuitous mutations of genes and a utilitarian selection. But this genetic hypothesis is again entirely beside the mark, for it does not touch the fundamental problems of the taxonomic system nor the taxonomic series with which the systematist has to deal. No simple external physical agent postulated as a fundamental cause of evolution, as X-rays, cosmic rays, ultra-violet rays, etc., can receive any serious consideration from any biologist who has some general knowledge of the organic kingdom; because it is evident that it is impossible logically to depend on random and universal agents, like the various radiations, to account for the fundamental fact of orthogenetic series when these series show no zonal arrangement in relation to supposed causal agents. It is a well-known fact that in ecological zonation of plants there can be, and usually is, a haphazard assemblage of diverse taxonomic types in the same zone which in itself shows that the taxonomic structures have neither been produced as a result of the environment nor been arranged in the zones because of taxonomic relation.

Any theory of evolution worthy of the consideration of any serious-minded biologist must also take account of the fundamental biological realities which go much deeper than the mere matter of speciation.

ORTHOGENETIC SERIES IN PLANTS

One of the decided and oft-repeated orthogenetic series to be observed in the flower is the progressive reduction of the floral members until the determinate limit is approached or reached for some essential organ. In the Alismatales, for example, *Echinodorus radicans* (Nutt.) Engelm. has about 20 stamens; species of *Lophotocarpus* have 15–9; *Helianthium*

parvulum (Engelm.) Small has 9; *Alisma plantago* L. has 6; *Potamogeton* species have 4; *Ruppia maritima* L. has 2; *Zannichellia palustris* L. and species of *Naias* have but a single stamen in the staminate flower. In this series the progression is to completely submerge plants and hydrophilous pollination, from an aerial habitat and entomophilous pollination. Now, in the anemophilous, aerial grasses, most of the bamboos have 6 stamens or sometimes even more to the flower; *Arundinaria* and the lower herbaceous grasses have 3, *Andropogon scoparius* Mx. has 3, *Andropogon elliottii* Chapm. has 1. Various entomophilous groups show the same sequence. In the Orchidales, *Thismia* has 6 stamens, *Neuwiedia* 3, *Cypripedium* 2, *Arethusa* and hundreds of other orchid genera have 1. In the Scitamimales, *Ravenala* has 6 stamens, *Musa* sp. 5, *Hedychium* and *Alpinia* 1, *Canna* and *Maranta* have only a half fertile stamen in the flower. Such series appear in numerous other monocotyl groups. Thus it will be seen that whether the plants pass under the water or remain in aerial conditions, whether the flowers are bisporangiate or monosporangiate, whether pollination is hydrophilous, anemophilous, or entomophilous, the results are the same in the evolutionary series in so far as the stamens are concerned. Neither the series as a whole nor any special member of the series shows any relation to the environment nor any advantage or disadvantage of one type over another. All of these species with one or with a half stamen are successful. There is no such thing as adaptation or utility in evidence as having any causal relation to the series. The same condition of things is evident in many lines of dicotyls. Taking for example a common dry land weed series in the Centrospermae: *Agrostemma githago* L. has 10 stamens, *Alsine media* L. 10–2, *Chenopodium album* L. 5, *Chenopodium rubrum* L. 2–1, *Monolepis nuttalliana* (R. & S.) Greene 1.

In certain groups the embryos of various species make a progressive series from straight to very decidedly coiled. A series in which the embryos develop under water is as follows: *Naias flexilis* (Willd.) R. & S. embryo straight, *Potamogeton heterophyllus* Schreb. embryo curved, *P. compressus* L. embryo slightly spiral, *P. diversifolius* Raf. embryo coiled, *P. dimorphus* Raf. embryo spirally coiled. This series may be compared with a series of common weeds of dry fields: *Polygonella americana* (F. & M.) Small, embryo straight or nearly so, *Rumex* sp. embryo slightly curved; *Polygonum* sp. embryo curved; *Cheno-*

podium ambrosioides L. embryo curved in an incomplete ring; *C. album* L. embryo forming a complete ring; *Sarcobatus vermiculatus* (Hook) Torr. embryo coiled into a flat spiral; *Salsola pestifer* Nels. embryo coiled into a conic spiral. The degree of coiling has neither significance of advantage or disadvantage in itself nor in relation to the environment. The two series occur in the two most extremely diverse ecological conditions imaginable. No "natural selection" nor utilitarian response to the environment had anything to do as a causal agent with the result.

Various monocotyl groups show a progressive union of the perianth segments. In *Aloe haworthioides* Bak. and *A. pratensis* Bak. the perianth segments are entirely free; in *A. myriacantha* (Haw.) R. & S. the perianth segments are only slightly united at the base; in *A. chloroleuca* Bak. the segments are united about one-fourth; in *A. somaliensis* C. Wright they are united about one-third; in *A. rubrolutea* Schinz the segments are united one-half; in *A. shimperi* Todaro they are united two-thirds; in *A. marshallii* W. & E. they are united three-fourths; and in *A. leptophylla* N. E. Brown the perianth segments are united more than four-fifths of their length. Nearly all of these species are South African.

In the Eriocaulaceae, there is a characteristic orthogenetic series in the change from ordinary petals to petals changed to a pappus or mass of hairs. This series is well represented by the petals of the carpellate flowers of the following species: 1, *Eriocaulon guianense* Koern.; 2, *E. longifolium* Nees.; 3, *E. crassiscapum* Bong.; 4, *E. woodii* N. E. Br.; 5, *E. majusculum* Ruhl.; 6, *E. griseum* Koern.; 7, *Lachnocaulon anceps* (Walt.) Morong. The extreme forms give an unusual type of flower with the petals represented by hairs between the calyx and gynecium. The sepals may also be similarly affected; but usually to a much less degree than the petals.

A common character in many genera of grasses is the presence of an awn on the lemma. These awns are of various lengths from mere points to structures of decided prominence. Thus in the genus *Bromus* the following series is to be observed: *B. inermis* Leyss has no awn; in *B. unioloides* (Willd.) H. B. K. the lemma has an awnpoint less than 1 line long; *B. kalmii* Gr., awn 1–1½ lines long; *B. purgans* L., awn 2–3 lines; *B. asper* Murr., awn 3–4 lines; *B. secalinus* L., awn 4 lines but sometimes awnless; *B. patulus* M. & K., awn 4–5 lines; *B. sterilis* L.,

awn 6–9 lines. A number of species of *Agrostis* in eastern North America have awns as follows: *A. perennans* (Walt.) Tuck. has no awn on the lemma; *A. hyemalis* (Walt.) B. S. P., sometimes awnless, sometimes with a very short awn; *A. geminata* Trin., awn 1 line long or less; *A. canina* L., exserted awn 1–2 lines; *A. borealis* Hartm., awn 2–2½ lines; *A. elliottiana* Schultes, awn 3–4 lines. *Festuca*, *Elymus*, *Muhlenbergia*, *Oryzopsis*, and *Andropogon* present similar conditions. Why these various specific lengths of these appendages? They are of no advantage or disadvantage. The species without awns are just as successful as those with awns; the short-awned species are just as good as the long-awned. But the orthogenetic series is definitely present and it must be considered without any fantastic hypothesis of teleological adaptation. To claim that such structures are of selective value presents the height of philosophical credulity; to see in them a response to environment is equally absurd. Nevertheless the evolutionary process is such that awns are evolved in the various species and these awns appear in various lengths, making the orthogenetic series.

The pods in the Brassicales are sometimes sessile and sometimes stalked. The stalks are also developed in various lengths. Brassicaceae—*Alliaria alliaria* (L.) Britt. has the pod sessile in the calyx; *Thelypodium integrifolium* (Nutt.) Endl., pod short-stipitate; *Stanleya pinnata* (Pursh) Britt., pod long-stipitate. Capparidaceae—*Polanisia graveolens* Raf., pod sessile in the calyx; *Cristatella jamesii* T. & G., stalk of pod 2 lines long; *Cleomella angustifolia* Torr., stalk of pod 3–4 lines; *Cleome serrulata* Pursh, stalk of pod 6–8 lines; *Cleome spinosa* L., stalk of pod 2–6 inches long.

In the evening primrose family as well as in some other groups, the epigynous hypanthium develops from nothing up to 7 inches or more in length. The following represents a series of various lengths: *Jussiaea* and *Chamaenerion* have no hypanthia; *Kneiffia linifolia* (Nutt.) Spach., hypanthium less than ¼ in. long; *Kneiffia longipedicellata* Small, hypanthium ½ in.; *Oenothera oakesiana* Robb., hypanthium 1 in. long. *Oenothera biennis* L., hypanthium up to 1½ in long; *Taraxia breviflora* Nutt., hypanthium up to 2 in. long; *Pachylophus canescens* Piper, hypanthium 3 in. long; *Oenothera longissima* Rydb., hypanthium 4 in. or more long; *Megapterium missouriense* (Sims) Spach, hypanthium up to 6 in. long; *Pachylophus caespitosa* (Nutt.) Rain., hypanthium up to 7 in.

long. A similar condition is represented by species of the Amaryllidaceae. *Leucojum vernum* L. has no perianth tube; in *Lophiola americana* (Pursh) Cov. the perianth segments are slightly united at the base; *Narcissus pseudo-narcissus* L. has a definite hypanthium ½ in. long; *Narcissus odorus* L., hypanthium ¾ in.; *Narcissus poeticus* L., hypanthium 1 in.; *Cooperia drummondii* Herb., hypanthium 1½ in.; *Hymenocallis occidentalis* (LeC.) Kunth, hypanthium 2 in.; *Crinum asiaticum* L., hypanthium 2¾ in.; *Hymenocallis macrostephana* Bak., hypanthium 3 in.; *Crinum amabile* Don., hypanthium 4 in.; *Hymenocallis kimballiae* Small, hypanthium 6½ in.; *Hymenocallis collieri* Small, hypanthium up to 7½ in. long. Again we see a gradation series of lengths in the same genus or closely related genera and in the same general environment. The moths, butterflies, and other insects get nectar from these tubes provided they have a proboscis or tongue long enough to fit the given case or can tear the tube open. But whether they obtain nectar or not, the mere act of alighting on the flower will induce pollination, since the stigmas and anthers are at approximately the same level above the tube of the hypanthium. Moths could survive because as the orthogenetic process brought out all sorts of lengths of probosces in the insects a similar orthogenetic movement was bringing out endless sorts of flowers with longer or shorter tubes, and it is evident that a moth with a long proboscis can very readily sip nectar from a flower with a very short tube as well as from one with a long tube. These orthogenetic series of nectar tubes have no significance in survival. To indulge in fantastic teleological speculations in respect to these developments does not explain why the whole orthogenetic series survived nor the fact that many flowers without nectar tubes or nectar are still visited by numerous insects bent on gathering pollen.

The Orthogenetic Series in the evolution of the solid or adnate hypanthium in Iris shows conclusively that the hypanthium in Iris was not produced as a "special adaptation" to prevent "unbidden guests" from pilfering the nectar reserved for moths with long probosces. The nectar is at the top of the solid hypanthium in this case.

1. *Iris xiphium* L. has no hypanthium. 2. *I. sibirica* L. has a tubular hypanthium ⅛–¼ in. long with no solid lower portion. 3. *I. ensata* Thunb. has a hypanthium ¼ in. long, the lower ⅛ in. being solid. 4. *I. versicolor* L. and *I. pseuda-*

corus L. have hypanthia about ½ in. long, ¼ in solid, and ¼ in tubular. 5. *I. chamaeiris* Bertol. has a hypanthium 1 in. long. 6. *I. cristata* Ait has a hypanthium 2¾ in. long, the solid portion being 2½ in. and the upper tubular portion ¼ in. 7. *I. reticulata* Bieb. has a hypanthium 3 in. long. 8. *I. unguicularis* Poir. has a hypanthium up to 6 in. long.

In addition to developing hypanthia, the species of Narcissus evolved a new structure, the crown, on top of the hypanthium. Since this is a new morphological structure, the evolutionary movement also brings out crowns of various lengths in an orthogenetic series independently of the length of the hypanthia on which they develop. *Crinum asiaticum* L. has no sign of a ridge or crown on the top of the hypanthium; *Narcissus jonquilla* L. has a short crown not over ⅛ in. long; *N. triandrus* L., crown ¼–½ in.; *N. pseudo-narcissus* L., wild variety, crown 1 in. long, cultivated varieties, crown up to 2 in. long. All the many species and varieties of *Narcissus* have crowns ranging within this series.

In the Ranunculaceae, various genera develop nectar pits or spurs on the petals, while other quite similar genera have no pits or spurs. The nectar spurs are prominent in *Aquilegia*. Just as in the case of length of awns or length of hypanthia these nectar spurs form an orthogenetic series. In the genus *Anemone* there are no nectar pits on the perianth segments. *Myosurus minimus* L. and species of *Ranunculus* have small pits at the base of the petals about 1 line deep; *Heleborus viridis* L. has petal tubes 2 lines deep; *Aquilegia eastwoodiae* Rydb. has the petals merely saccate, not spurred; *A. brevistyla* Hook. has nectar spurs about 3 lines long; *A. glandulosa* Fisch., nectar spurs 3–6 lines; *A. sibirica* Lam., nectar spurs 6–9 lines; *A. canadensis* L., nectar spurs 8–10 lines; *A. formosa* Fisch., nectar spurs 9–12 lines; *A. skinneri* Hook., nectar spurs 1½–2 in.; *A. chrysantha* Gr., nectar spurs 2–2½ in. long; *A. longissima* Gr. has a spur 5 in. long. As in the evening primrose, the pollination does not depend on whether the insect can reach the nectar in the bottom of the spur. If the insect alights on the flower, pollination will be accomplished. In this connection one may recall the fantastic notions of "favored and unbidden guests." I have seen bumblebees and honeybees attempting to get at the nectar of the long-spurred columbines without success, but in the meantime pollination was accomplished as readily as if a long-proboscis hawkmoth had hovered over the flowers and sipped the cup of nectar.

One meets with orthogenetic, perfection series in many different types of structure. The glandular pits on the backs of the leaves of species of *Cupressus* show such a series. *Cupressus goveniana* Gord. has glandless leaves; *C. macrocarpa* Hartw. has the leaves glandless or obscurely pitted; *C. guadalupensis* S. Wats., leaves with a dorsal pit but not resin-glandular; *C. macnabiana* Murr., leaves with a conspicuous gland on the dorsal surface secreting resin; *C. glabra* Sudw. leaves with a very conspicuous resin-secreting gland on the back.

There is an orthogenetic series in relation to those extraordinary developments, the pollinia, in the Orchidales. *Thismia hyalina* (Miers) B. & H. has round, smooth pollen grains of the ordinary type. In the main subfamily of Orchids, the Orchidatae, *Cephalanthera grandiflora* (Scop.) Bab. also has granular pollen of the ordinary type. *Arethusa bulbosa* L. has powdery-granular pollen; *Corallorrhiza wisteriana* Conrad, pollinia soft waxy without a caulicle; *Liparis liliifolia* (L.) Rich., pollinia two in each anther sac smooth and waxy, in pairs slightly united but without a stalk, thread, or gland; *Tipularia unifolia* (Muhl.) B. S. P., pollinia ovoid, two in each anther-sac, separate, affixed to a short stipe which is glandular at the base; *Coeloglossum bracteatum* (Willd.) Parl., pollinia oblong-ovoid, with a long caulicle having a glandular base but scarcely wider than the caulicle; *Galeorchis spectabilis* (L.) Rydb., pollinia oblong, granulose, one in each anther-sac, with a slender caulicle having a large glandular disc at its base; *Lysias orbiculata* (Pursh) Rydb., pollinia with a prominent caulicle having an orbicular glandular disc at its base. Thus we see within the closely related plants of a single subfamily a closely graded perfection series of this extraordinary structure and the degree of perfection has nothing to do with survival of the species and there can be no selective action because the whole series is present from zero to the highly elaborated mechanism. In the Apocynaceae-Asclepiadaceae there is a somewhat similar progression from waxy pollen to the highly elaborated pollinia of Asclepias.

In the genus *Araucaria*, the widths of the leaves of the various species form an orthogenetic series from *A. araucana* (Mol.) Koch. with large broad leaves, thru *A. bidwillii* Hook. and *A. cunninghamii* Ait. to *A. excelsa* R. Br. with awl-shaped, vertically compressed leaves. Similar series occur in a number of other groups of Conifers. There is also a progressive series

of leaf widths in the *Populus-Salix* group from very broad to very narrow, as illustrated by the following species: *Populus deltoides* Marsh., *P. italica* Moench, *P. alba* L., *P. acuminata* Rydb., *Salix lucida* Muhl., *S. pentandra* L., *S. amygdaloides* And., *S. nigra* Marsh., *Populus angustifolia* James, *Salix interior* Row. The last two "mimic" each other very closely in size, shape, surface, and petiole length. Mimicries are the result of parallel or duplicate orthogenetic evolutions or sometimes of a mere accidental development of form, color, or structure, sometimes in closely related groups, sometimes in groups far apart in relationship, sometimes in the same geographic region, sometimes in regions widely separated. There is no evidence of "mimicry" in the old teleological sense. Such speculations, indulged in at great length by the older school of selectionists, were merely fantastic exercises of the imagination of the same scientific import as the imaginary designs of birth marks of fruits, leaves, seeds, plum pits, flames, etc., which the superstitious believe are caused by strong mental impressions of the mother during pregnancy. There is no more scientific evidence for a belief in selective mimicry than there is for the supposed prenatal influence of the mother's mind in determining birth marks.

In various groups there is an orthogenetic series in the development of the lobing of the petals, ranging from petals with rounded tips to very deeply divided petals. Such a series is present in the chickweed alliance as shown by the following: *Arenaria stricta* Mx., *A. hookeri* Nutt., *Cerastium semidecandrum* L., *Alsine holostea* (L.) Britt., *A. longipes* (Goldie) Cov., *A. media* L. (Fig. 1). Certainly no one with any knowledge of ecological relations would believe that any of these notched, lobed, or divided petals which make up the series are of any special advantage or environmental "adaptation."

The remarkable insectivorous leaf of *Drosera rotundifolia* L. has been widely exploited by teleologists. There is no question about its seemingly perfect "adaptation" for catching small insects. But when the genus is studied as a whole, *D. rotundifolia* is found to be but the end of an orthogenetic series, the preceding members of which, especially the first ones, are poorly fitted for catching insects. In fact the lowest are no more successful in this respect than great numbers of plants which have glandular or glutinous hairs or surfaces on the leaves or stems or in the inflorescence. A good series is represented by

the following species: *Drosera filiformis* Raf. with slender filiform leaves as the name implies; *D. linearis* Goldie, leaf blades linear; *D. longifolia* L., blades elongated spatulate; *D. intermedia* Hayne, blades short spatulate; *D. rotundifolia* L., leaf blades orbicular, abruptly narrowed into a flat, pubescent petiole. Thus it is seen that there are all degrees of this peculiar "adaptation" and that all have survived in their bog habitats. There has been no selection of the fittest at the expense of the less fit or the decidedly unfit in respect to the ability to catch insects. There has been no similarity in leaf form or perfective mechanism in relation to environment, but there has come out of the evolutionary process a very interesting orthogenetic series, and this series exists and calls for consideration no difference whether it evolved, step by step,

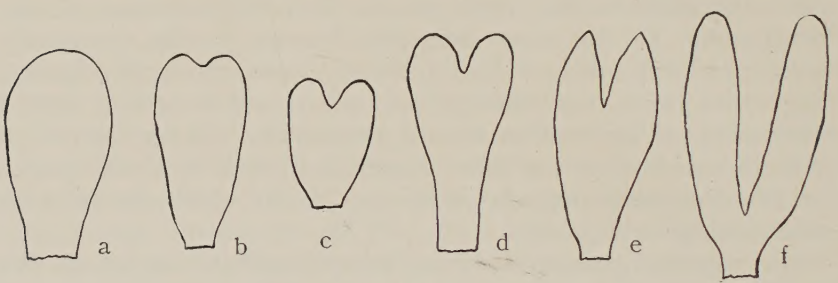

Fig. 1. Orthogenetic series in the division of the petal of closely related species in Caryophyllaceae. a, Entire petal of *Arenaria stricta* Mx. b, Slightly emarginate petal of *Arenaria hookeri* Nutt. c, *Cerastium semidecandrum* L. d, *Alsine holostea* (L.) Britt. e, *Alsine longipes* (Goldie) Cov. f, Divided petal of *Alsine media* L.

in the direction toward the perfected devise, or whether the members of the series mutated in an irregular manner. Finally it is doubtful whether there is any real advantage to the plant in the capturing of insects or other small creatures.

The evolution of the inflorescence also produces progressive series in many groups, as for example, in *Acer* and *Prunus*. *Acer pennsylvanicum* L. has a receme; *A. platanoides* L. a corymb; *A. saccharum* Marsh. an umbellate corymb; *A. saccharinum* L. an umbel-like cluster. *Prunus virginiana* L. has a raceme; *P. mahaleb* L. a corymbose inflorescence; *P. americana* Marsh. an umbel or fascicle; *P. spinosa* L. umbel reduced to 1–2 flowers.

One of the most peculiar and extreme types of fruits is the syconium or fig-fruit of the Common Fig, *Ficus carica* L.,

which represents a hollow or bottle-like, fleshy stem or inflorescence receptacle with the apex of the stem at the base of the cavity and with numerous flowers on the walls within. This type is a long distance away from the common type of fleshy ament as in species of *Morus*. In this case also the fig fruit does not represent a survival by selection or direct response to environment through the elimination of the less fit but is the end product of an evolutionary movement which produced another remarkable orthogenetic progression, practically all the general steps in the series being represented by living representatives. A few years ago it was the writer's good fortune to see a number of the species of the series in fruit at the Kew Gardens, England. The series may be illustrated by the following species: *Morus alba* L., *Dorstenia psilurus* Welw., *D. yambuyaensis* De Wild; *D. arifolia* Lam., *D. alata* Gardn., *Ficus carica* L. The fruit of *Dorstenia elata* Gardn. is a deep cup-like receptacle, while as is well known the fruit of *Ficus* has only a minute opening at the tip.

Various groups of plants show series of progressive flattenings of the stem and the development of two lateral wings from the ordinary cylindrical type. Such a series was outlined in a former paper of the "STUDIES." Extreme flattenings are represented by *Sisyrinchium grammoides* Bickn. and *Marica gracilis* Herb. belonging to the Iris Family. The genus *Lathyrus* of the Bean Family also shows species with progressive flattening of the stem with two wings as follows: *Lathyrus maritimus* L. and *L. venosus* Muhl. have the stem angled but not winged; *L. palustris* L. and *L. macranthus* (White) Rydb. have the angled stem slightly winged; *L. pusillus* Ell. and *L. grandiflorus* Sibth. and Sm. have the stem winged; *L. odoratus* L. has the stem prominently winged; *L. latifolius* L. has the stem broadly winged.

In various groups of Cacti there are progressive series from cylindrical to decidedly flattened stems, in the extreme types associated with a 2-ranked phyllotaxy. *Opuntia imbricata* (Haw.) Engelm., a tree Prickly-pear, has cylindrical stems; *O. fragilis* (Nutt.) Haw. joints somewhat flattened; *O. macrorrhiza* Engelm. joints decidedly flattened; *Epiphyllum oxypetalum* (DC.) Haw. (*Phyllocactus latifrons* Link) branches flat and thin, *Zygocactus truncatus* (Haw.) Schum., Christmas Cactus, joints exceedingly flattened and thin. In the genus *Ripsalis* there is a series of species from *R. virgata* Web. with

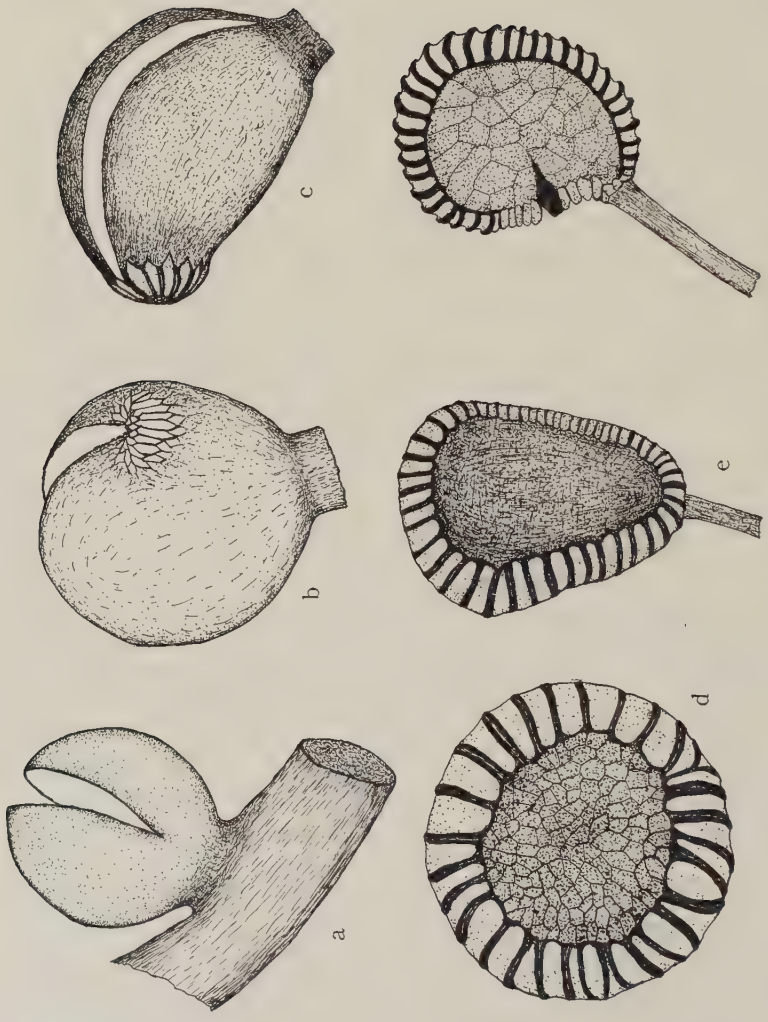

Fig. 2. Orthogenetic series in the evolution of a spore-throwing mechanism in the ferns. a, Sporangium of *Botrychium obliquum* Muhl. b, *Osmunda regalis* L. c, *Aneimia tomentosa* Sw. d, *Gleichinia longissima* Blume. e, *Cibotium chamissoi* Hk. & Bkr. f, *Onoclea sensibilis* L.

cylindrical stems to more and more flattened-stem forms, until in *R. elliptica* Lundb. and *R. russellii* Britt. and Rose the joints are very flat and thin.

Even the evolution of the mycorrhizal inter-relationship of fungus and root may show an orthogenetic series. J. Ramsbottom[1] in his study of mycorrhiza in the heaths says: "In the root-tip region we get an ascending series in the amount of fungus present from *Chimaphila umbellata* where the epidermal cells of some roots are without hyphae and other roots with hyphae, but not in every cell, to *C. maculata* with a greater number of the epidermal cells filled with hyphae; in *Pyrola rotundifolia* and *P. elliptica* all the cells are infected and there is the beginning of intertwined hyphae round the root tip; then in *Monotropa hypopitys* an increase in the width and extent of the sheaths and a division into two zones—an outer loosely woven mass of hyphae and an inner more compact one—and finally in *M. uniflora* a still greater width of the fungal sheath. In the least saprophytic species the epidermis soon dies off, carrying with it the fungal hyphae as in Chimaphila and Pyrola, whereas in Monotropa, especially *M. uniflora*, the epidermis is still living and filled with hyphae when the root is quite old. Corresponding with this increase in saprophytism there is an increase in the number of seeds produced and a reduction in their size and structure." It will be noted that a loss of chlorophyll is also involved in the more advanced species and that the simplification of the plant body and inflorescence and leaf structures attain their extreme limit also in *M. uniflora*.

AN ORTHOGENETIC SERIES LEADING TO A HIGHLY PERFECTED MECHANISM OF NO SURVIVAL VALUE TO THE INDIVIDUAL

The ferns have evolved a series of sporangia which represents a progression toward perfection in a mechanism which throws out the mature spores suddenly, by means of a hygroscopic ring of cells around the sporangium. The extreme type represents a very efficient and elaborately perfected structure which does the plant no good, for those species which are at the bottom of the series are just as successfully distributed as those with the perfected mechanism. Such a series is illustrated in Fig. 2. *Botrychium obliquum* Muhl. has a

[1]Ramsbottom, J. Trans. British Mycol. Soc., **8**: 28–61. 1923.

sporangium which merely opens by a simple slit and the spores fall out by accident (a). In *Osmunda regalis* L. the sporangium is nearly the same shape, also with a vertical slit, but at one side at the end of the dehiscence slit there is a peculiar group of cells with thickened walls (b). This group of cells represents the first step in the evolution of a remarkable structure, the annulus. So far as spore scattering is concerned, *Botrychium* can scatter its spores just as readily as *Osmunda* with the special patch of cells in the wall of the sporangium. In *Aneimia tomentosa* Sw. there is a decided advance in the group of thick-walled cells over that in *Osmunda* and is now arranged in the form of a ring at one end of the sporangium, the dehiscence still being by a vertical slit (c). In *Gleichinia longissima* Blume the sporangium has a complete ring of highly specialized cells (d). The figure represents a sporangium from the top. In *Cibotium chamissoi* Hk. and Bkr. there is also a complete ring which passes vertically around the sporangium to one side of the stalk (e). The cells on one side of the ring are much more elaborately developed than on the other. This sporangium is approaching the ideal type developed in the Polypodiaceae. In *Onoclea sensibilis* L. and many other Polypodiaceae there is a highly evolved incomplete ring with special lip cells on one side and cells with extremely hygroscopic walls on the other (f). When the sporangium is mature the hygroscopic ring, by turning back and straightening out, tears the sporangium open gradually but quickly and then suddenly collapses again with a jerk, thus throwing out the spores. A more perfect and ingenious mechanism for the purpose, and with the limited material employed, can hardly be imagined; but this perfected spore thrower is of no importance to the fern in giving it any advantage in distribution or survival. *Botrychium virginianum* (L.) Sw. is just as widely distributed and just as abundant if not more so, as *Onoclea sensibilis* L. It will be noted also that *Onoclea* has the pinnules which bear the sporangia rolled up into berry-like segments, which although they open up at maturity nevertheless must interfere decidedly with the scattering of the spores by the annulus mechanism. In the Hawaiian fern, *Cibotium chamissoi* Hk. and Bkr. the indusium forms a thick-walled box-like two-lobed structure with one lobe forming an open valve or lid for the other which holds the cluster of sporangia. Although the lid of the box opens up at maturity, this highly developed indusium must interfere decidedly with

the free discharge of the spores in the same way as the enrolled pinnule of *Onoclea*. At best, even with no special obstruction, the spores can be thrown only a short distance and their wide distribution is accomplished by wind, water and animals, which carry the spores of ferns like Botrychium without any throwing device as effectively and as widely as those with the perfected spore-throwing mechanism. The highly elaborated spore-throwing sporangium then is of no advantage to the plants which possess it but simply represents the end product of a perfective, evolutionary, orthogenetic series which came to perfection through intrinsic processes and causes.

SOME SIMPLE ORTHOGENETIC SERIES OF ANIMALS

Plants and animals form one organic system and the laws of heredity and evolution are the same fundamentally for both kingdoms. Since the higher plants are simpler in their organography and anatomy and especially since most plants have indeterminate and repetative growth, they are more convenient and reliable for the discovery of the true nature of heredity and evolution in general than the animals with their rapidly determinate ontogeny, which in all the higher forms do not give rise directly to new individuals by a normal process of budding and continuous growth as is common in plants. However, when one examines series of related animal species, either in the paleontological record or by a comparison of living forms, one finds on every side the same kind of orthogenetic series in the evolution of organisms and tissues as in plants. A few examples will be considered below for comparison with plant series. The presence of orthogenetic series was first studied intensively by paleontologists who could not escape the very clear cases presented by the degrees of coiling of Cephalopod shells, the development of complexity of the sutures in the shells of Ammonoids, the progressive change in the feet of the ancient horse series, the progressive evolution of the cusps of the teeth of mammals, and numerous other paleontological problems of a similar nature.

The Lamellicorn Beetles (Scarabaeidae) have a peculiar backward-projecting horn on the head or thorax which is evolved in various lengths in different species. *Canthon laevis* has no horn on the head or thorax. In *Copris tullius* the female has a short tubercle on the head and the male has a short horn. In *Xyloryctes satyrus* the female has a slight point on the head

and the male has a horn of medium length. In *Copris arizonensis* the female has a short spatulate horn on the head and the male has a prominent horn. In *Phanaeus carnifex* the female has a short blunt tubercle on the head while the male is provided with a long curved horn. In *Phanaeus quadridens* the female has a short blunt point on the head while the male has a very long horn. So all the horns of the males of these beetles and their relatives form a close orthogenetic series of lengths which give no advantage to the individual possessing the one type or another. The notion of special adaptation is not to be entertained rationally. The sex dimorphism present in these species was not originated because the female delights in a mate with long horns or because he can protect her and himself but because the two sexes are on a different metabolic level. Exactly similar phenomena can be observed between male and female structures in plants. Thus in the monecious *Zizania aquatica* L. the staminate spikelets are awnless while the carpellate spikelets have long awns.

The long-horned Wood-boring Beetles (Cerambycidae) as well as many other groups of insects present an orthogenetic series in the lengths of their antennae. *Moneilema varolare* and *Xylotrechus colonus* have rather short antennae, considerably shorter than the body. *Acanthocinus spectabilis* and *Monochamnus notatus* have antennae much longer than their bodies. Other long-horned wood-boring beetles take their positions in this series with all sorts of lengths of antennae. These various lengths are of no special value, but after the beetle has antennae of a given length it, of course, must accommodate its life and movements to the restrictions, advantages, or disadvantages of the length possessed or be eliminated in the struggle if the given length has any determinate effect, which seems improbable since the whole series of lengths has proven successful.

Among the important structures present in some groups of moths is the proboscis which also comes in series from zero to a structure of great length in the hawk moths (Sphingidae). The proboscis consists of the greatly lengthened maxillae and is useful for sucking nectar from flower cups and spurs. The lowest types of moths do not have a sucking proboscis. In *Sabatinca* sp. (Micropterygidae) the mandibles are functional dentate organs. In *Eriocrania* sp. (Micropterygidae) the mandibles are non-dentate and the terminal joint of the galea of either side is opposed to that of its fellow, thus exhibiting

the first step in the formation of a proboscis. In some forms of the Sphingidae the proboscis is also represented by a pair of tubercles, which is usually considered as representing a reduced condition, but there is no evidence that it was ever derived from an originally highly evolved proboscis. Now from these primitive conditions there are moths with proboscis of all sorts of lengths. *Protoparce quinquemaculata*, the common tomato-worm moth, has a proboscis 5–6 inches long. In *Cocytius proboscis* the proboscis is said to attain the enormous length of 10 inches. Here then is a remarkable orthogenetic series of lengths of an essential organ which runs parallel with various series of lengths of corolla tubes and spurs. Of course, it is evident that the moths with the longest probosces can sip nectar from the longest flower tubes and spurs, but they can and do also gather the nectar from flowers with comparatively short tubes. And such flowers are much more common in all areas than those with very long tubes. Thus the long proboscis has not evolved thru any adaptive necessity, and as stated above the flower with long tubes and spurs will be pollinated by the general swarm of pollen and nectar eating insects whether they are lucky enough to reach the nectar or not.

In various groups of wasps the thorax is separated from the abdomen by a slender connective or peduncle. This extraordinary structure which separates the front end of the body from the back end also comes in an orthogenetic series, as might be expected. In *Sphecius speciosus* the thorax and abdomen are contiguous. In *Chrysis ignita* there is no prolongation of the connective but nevertheless a distinct separation of the thorax and abdomen. *Prionony x atrata* has a short connective. *Chlorion coeruleum* has a connective about one-half as long as the abdomen. *Eumenes petiolata* has a connective longer than the abdomen. *Ammophila sabulosa* has a connective about twice as long as the abdomen. To see any special advantage in such a condition is to proclaim one's self a firm believer in witch stories and fairy tales.

Mammals exhibit orthogenetic series in the lengths of their tails. Among the Ground Squirrels, the California Ground Squirrel (*Otospermophilus grammurus beecheyi*) has a tail 7 in. long. The Yukon Ground Squirrel (*Citellus osgoodi* has a tail 5–6 in. long. The Franklin Ground Squirrel (*Citellus franklini*) has a tail 5 in. long. The Apache Ground Squirrel (*Citellus spilosoma macrospilotus*) has a tail 3 in. long. Other

species of Citellus and other genera of ground squirrels have tails of various lengths which can all be arranged in orthogenetic series and have no relation to advantage or disadvantage to the animals in their various geographic regions and habitats.

The Lemurs live mostly in Madagascar. Their tails, which are never prehensile, show a very striking orthogenetic series. Three species which are nocturnal tree-dwellers have tails as follows: *Indrus brevicaudatus* has practically no tail. *Lepidolemur microdon* has a tail a little over one foot long. *Lemur fulvus* has a tail two feet long. There is no more reason for looking for an external cause as the driving force of evolution to explain the series of tail lengths of these animals than there is for looking for a driving force to explain the numerous series of compounds of organic substances outside of the atoms and particles that make up these compounds.

The tails of monkeys also represent orthogenetic series, from no external tail at all to very long appendages; and it will make no difference how we assume the series to have evolved, whether from short tails to long tails, from long tails to short tails, or from an original medium length tail in both directions, the fact of the series is still present and represents the result which the ultimate cause of the evolutionary movement has brought about, with no reference, directly, to utility or advantage or disadvantage in relation to survival. The Platyrrhines, which are exclusively New World monkeys, have various lengths of tails and some are prehensile and some are not. Some species in the family Cebidae have very short tails but more commonly the tails are long and often prehensile. In the genus *Cebus* the tail, though prehensile, is covered with hair to the tip, being thus a less perfect grasping organ than is the case with those monkeys which have a naked under surface to the prehensile end of the tail. This prehensile tail attains its greatest perfection as a "fifth hand" in the spider monkeys (Ateles), probably the most typically arboreal monkeys of America. Short-tailed American monkeys are species of the genus *Brachyurus*. So these monkey tails form orthogenetic series both in respect to lengths and also in respect to perfection as prehensile organs, from no prehensibility through various degrees to the extremely perfected prehensile tails of the spider monkeys. But these spider monkeys, being of comparatively light weight and slender build, should have the least use for these useful appendages in comparison with various other

more robust and heavy arboreal monkeys which have no prehensile tails whatever. The spider monkeys with their long legs and their perfected prehensile tails may be compared with the long-armed agile gibbons, like *Hylobates agilis*, which have no tails at all but which are among the most extreme of arboreal apes.

Now when one studies the Catarrhines, which are exclusively Old World monkeys, he finds no prehensile tails whatever, although they climb about on the trees just as the American monkeys do. These Catarrhines have tails of all sorts of lengths also making typical orthogenetic series from no external tail at all to some with very long tails. Thus *Presbytes melalophos*, the Simpai of Sumatra, has a tail nearly 3 ft. long, while the body of the animal is only about 1½ ft. long. *Cercopithecus diana* of Africa also has a very long tail. *Cercopithecus petaurista*, the White-nose Monkey of Western Africa, has a tail nearly 2 ft. long with a body measuring 15–16 in. *Cynocephalus mormon*, the Mandrill, has a short erect tail. *Cynopithecus niger*, of Celebes, has a very small rudimentary tail. *Macacus inuus*, the Barbary Ape of North Africa, has no external tail, and as stated above, the Agile Gibbon, an extremely active, arboreal species, also has no external tail. If the monkeys tails were originally long, why is there an orthogenetic series of lengths to complete disappearance in these Catarrhines when it is never of use as a grasping organ? Why did some of the American monkeys develop the prehensile ability while the old world monkeys acquired no such mechanism? Would a confirmed teleologist come to the conclusion that the American tropical forests were continuously subject to violent storms which made prehensile tails necessary while the Old World tropics were regions of perpetual calm which thus did not require the tree dwellers to evolve this "fifth" hand to keep from being hurled to earth and untimely death by "unkind mother nature?" The facts must be faced in their generality to see the real absurdity of the teleological explanations, whether Lamarckian or Darwinian. After a certain mechanism has evolved it may be of use to the organism but it could not be of special use until it had evolved to a rather decided stage of perfection. Imagine a poor, Old World monkey trusting for safety to his tail! This notion of adaptation is largely (in this case) a fairy tail. The tails are just not adapted to the trees. But it is remarkable how extremely some biologists are obsessed by the notion of *special adaptation*.

GENERAL CONCLUSION

The fact of orthogenetic series, both accumulative and perfective, plainly shows that the notions of specific adaptation and teleological causation have no scientific basis; since these series have no general correspondence with differential environments nor with any advantage to the individual. It is also clearly evident to the careful student of taxonomy in relation to evolution that the recognition of a perfective principle does not at all require the postulation of an entelechy as elaborated by Driesch and others. But the recognition of the orthogenetic series and of the perfective series as a result of the perfective principle in the organic kingdom does require us to recognize an internal creative principle which is just as evident and unescapable as the fact of the general atomic series and the complicated molecule systems of the chemist.

In addition to the evidence from orthogenetic series, further knowledge of the nature of the evolutionary process may be obtained from a study of the constancy attained at the limits of the series. This unchangeableness is well illustrated by the 4,000 species of grasses all of which have attained the two-ranked condition of the leaves and the unilocular ovulary. Both of these characteristics represent the possible determinate evolutionary limit. The same is true for the ten to fifteen thousand species of the subfamily Orchidatae, practically all of which have two-ranked leaves and also have a unilocular ovulary and a single stamen always occupying the same position in the flower. This constancy of the evolved structures which have attained the limit of the orthogenetic series shows how far from the mark are those speculations which see in the abnormal mutations caused by X-rays, radium, ultra-violet light, cosmic rays, etc., the fundamental cause of the evolution of the taxonomic system of plants and animals. The grasses and orchids and other such large culmination groups have been bombarded for millions of years by cosmic and other rays but the fundamental potentialities remain unchanged, although an enormous amount of subordinate evolution and speciation has been going on.

In recognizing the existence of an *internal* creative principle, science comes to its limit. The next step in causative reasoning, as to what is the ultimate cause of this orthogenetic, progressive, perfective principle, is a question of theistic philosophy and belongs to the domain of the philosopher rather than the

scientist. An anarchistic philosophy is definitely contradicted by the facts of the orderly taxonomic system in general and by the presence of the perfective, orthogenetic series in particular. The biologist, however, can recognize the fact of a *universal design* in nature as a scientific discipline and the remarkable success which the fundamental evolutionary activities have brought about in the *balance of nature*, which not only permits thousands of the most diverse types and species to come into existence but also allows, in spite of the struggle for life, endless numbers of species to continue successfully in the narrow shell of the earth's surface for millions of years.

The examples of orthogenetic series discussed in this paper, and which could be multiplied indefinitely, show again that evolution is intrinsic rather than extrinsic, kinetic rather than static; progressive, orthogenetic, and perfective rather than haphazard; and finally determinative in many of its characteristic movements.

Sterilization

This volume is a report of a special committee of the American Neurological Association appointed to study the question of Eugenical Sterilization from a medico-legal standpoint. Four of the authors are physicians, the fifth being a consultant in Genetics (Keeler). The book opens with a short history of sterilization, followed by a rather detailed summary of the laws of the various states and of some foreign countries. The main arguments for sterilization are reviewed, some of them being severely criticized by the authors. The data on the inheritance of various mental conditions are critically reviewed. A very short chapter on crime is included. The committee recommends that sterilization laws in the United States should be voluntary rather than compulsory, that they should apply to mental defectives in private institutions and at large in the state as well as to those in state institutions, that they should be administered by boards composed of persons with special training who are legally protected by statute, and that such laws should apply only to selected cases in the following conditions: Huntington's chorea and certain other disabling degenerative diseases recognized to be hereditary, feeblemindedness of familial type, dementia praecox, manic-depressive psychosis and epilepsy. The committee warns against the sterilization of normal persons for purposes of preventing the appearance in their descendants of undesirable mental traits, it frowns on the use of sterilization for immorality or character defect, it urges that environment be not lost sight of as important in the production of all traits, and finally the committee urges further co-ordinated research along these various lines. The style of the book is somewhat rambling and not completely unbiased, but the volume is nevertheless worthwhile, chiefly for its critical review of the literature.—L. H. S.

Eugenical Sterilization, by a Committee of the American Neurological Association. 211 pp. New York, The Macmillan Co., 1936. $3.00.

ADDITIONAL NOTES ON ARGULUS TRILINEATUS (WILSON)

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The female of this species was described by Wilson (1904) from specimens collected on goldfish in Georgia and Kentucky. Cockerell later identified them in Colorado and suggested that they might be closely related to *Argulus coregoni*. Guberlet described the males for the first time in 1928 from specimens taken on goldfish in Washington and California. Since that time they have been recognized in a great many places over the country, so that the distribution is quite extensive.

The present specimens were taken from goldfish, *Carassius auratus*, at Natchitoches, Louisiana. These have been compared with types 56568 loaned by the U. S. National Museum, and with *A. coregoni* sent by the British National Museum. Dr. Zacwilichowski of Jagelon University, Krakow, Poland, was kind enough to send female specimens of *Argulus foliaceous*, while Dr. Schellenberg of "Der Zoologisches Museum der Universität, Berlin, Germany, sent both males and females for comparative purposes. There has been no opportunity to examine the type for *A. trilineatus* (Wilson).

The one significant feature overlooked in the original description that sets the species apart from all others in America is that the ribs on the dorsal side of the carapace are forked as in the European species. Guberlet showed this in figure 1 of his monograph, but failed to mention it. Wilson (1903) stated that it is one of the characteristics distinguishing the European species since none of the American species which he had observed had such a modification.

To be sure the branches are not readily apparent on some specimens, but are very obvious on others. They are found on the specimens from the National Museum, as well as those from Louisiana. One can make them distinguishable by staining lightly with methylene blue. After it has once been called to attention, one can readily see, from the offset of the rib in the region of the base of the antennae, that the shape is such as to suggest the presence of a branch. This feature is

no more apparent on some specimens of *A. foliaceous* than on the American species. At the same time these ribs are definitely bowed inward between the eye and sucker regions and outward around the brain rather than nearly parallel as previously described. Figure 1 shows all of these characteristics.

A perusal of the European literature from 1800 on would lead one to suspect that *A. trilineatus* might be exactly like *A. foliaceous* except for size. An examination of the description and figures by Claus (1875), which seem to be the most complete, reveals that his description follows the American species almost identically. In his paper, figure 22 of the respiratory areas is identical with our species, figure 25 of the dorsal ribs is the same, figure 20 shows the antennae exactly alike, while figure 26 has four leaves between the ribs of the sucker and five to six plates in each of these ribs with the same shape as the local species. His figure 44 is a drawing of the accessory sex organs of the last two pairs of legs which might have been taken from American specimens. Even the spines on the comb and second and third segments of the second maxillipeds, which are different on each of the European species, are similar, so that all details described and figured are alike for *A. foliaceous* and *A. trilineatus*.

Although Claus has drawn a "peg" identical to that of the American species, the European specimens at hand are somewhat different. Figures 2 and 3 are drawings of the organs from the two; figure 2 is that of the American form. They do show a similarity, but are not as much alike as shown by him. On the German specimens at hand this structure is much less chitinous and does not become as spatulate. This would seem to indicate that both species have changed somewhat.

No mention was made in any of the European literature of the accessory organs on the second pair of legs of the male. Wilson (1904), in his description of *A. foliaceous*, states, ". . . Abdomen in the male considerably elongated, but no copulatory organs except the regular peg and semen vesicle. . . ." An examination of specimens shows that there is an accessory organ on these legs such as that shown in figure 4.[1] There is considerable difference between this and figure 5, which is the same organ on *A. trilineatus*. This structure is almost identical with that of *A. coregoni*.

[1]A paper by Wagler (1935) was called to my attention since gathering this data. It has a good figure of the organ (Fig. E, p. 8).

Communications with two European authorities state that there is confusion in the identification of the two native species. If they do actually intergrade, as one would be led to believe, it is very possible that the American form is derived from European stock not so far back. Such is indicated by the fact that they are found only on goldfish in this country, most of which are of European origin, and because it has some of the distinguishing marks of both of the species found there.

There are certain other features of *A. trilineatus* which have either been missed or not adequately described. Chief among these is the structure of the second antennae. Wilson definitely states that there are two distal segments (1904, p. 652 and fig. 26) and Guberlet says, "The basal joint of the second antennae is longer and thicker than the two distal joints." On all of the specimens examined, including those from the Museum, there are three distal segments as shown in figure 6. The apparent oblique direction of these segments that has been noted for some specimens, is wholly due to the fact that they are attached on the posterior edge of the basal segments and the direction is dependent upon the way they are flexed when the animal is killed. It is variable from specimen to specimen and probably is of no specific value.

On the first maxillipeds the ribs are composed of a series of plates similar to figure 7. These increase in size from the outer to the inner edge and number five or six with an additional basal plate supporting them on the inner rim. The number is variable even in the same appendage on some animals. The number of leaves along the outer edge of the disc, counting between the ribs, varies from five to eight, but five or six is the common number.

The respiratory areas are not exactly as figured by Wilson. They are somewhat narrower at the top than at the bottom with a depression on the side toward the body, so that the appearance is almost reniform. The anterior respiratory area is egg-shaped with the point toward the body and between the sucker and posterior respiratory area. These are shown in figure 8.

The accessory organs of the male have already been described. Martin (1932) made observations on the copulating animals and found that they are used for clasping rather than for the actual transfer of the sperms as some of the earlier authors have intimated. From the shape of the armature of

the organs figured in the literature, and from the fact that the genital openings are nowhere near them, it is easy to visualize the possibility that such is the case.

There seems to be no structure such as the "flattened bladelike" projection on the anterior border of the second pair of legs as described by Guberlet. The nearest approach to such a formation occurs in many instances where the musculature has pulled away from the exoskeleton on mounted specimens, but this is not confined to the second legs alone. There is a flat plate-like area between the second and third legs.

The pigment spots, from which the American species gets its name, are also found on *A. foliaceous* and are arranged in two double rows, one on either side of the abdomen. These are decidedly a more distinct characteristic of the female than of the male. The male is characterized by the large amount of pigment in the lateral canals extending out into the wings of the carapace on either side and dividing into two branches, one running forward and the other backward and dividing into numerous smaller lateral branches extending toward the outer edges. There are other species which have pigment along these canals. It is also found on the female but is not nearly so prominent.

Certain characters seem to be variable from one individual to the next. The carapace may reach the abdomen on some specimens and extend only to the third legs on others. There is some variation in the proportions according to the individual. There is variation in the size and length of the antennae. The number of plates in the ribs of the suckers may be different as well as the number of leaves between the ribs. On some specimens there is a definite cross rib between the joints of the dorsal ribs behind the brain, while on others it is not noticeable, but may be represented by a fold or be entirely lacking.

The striking similarity between *A. trilineatus* and *A. foliaceous*, including the branching of the dorsal ribs, definitely marks the American species as being of European origin. The shape of the peg, which is one of the specific characters, is similar. Such small details as the setae on the second maxillipeds, the number of plates in the ribs of the sucker, and the number of leaves between them are almost identical. The European species has a slightly different type of armature on the second legs in the male and lacks the flat protuberance between the second and third legs which is so characteristic of

the American form. The females of the two species are alike. If there is as much variation within the European species as is shown by Claus' figures and as compared with the specimens examined, then there is less difference between the species of the two continents than there is between the two from Europe.

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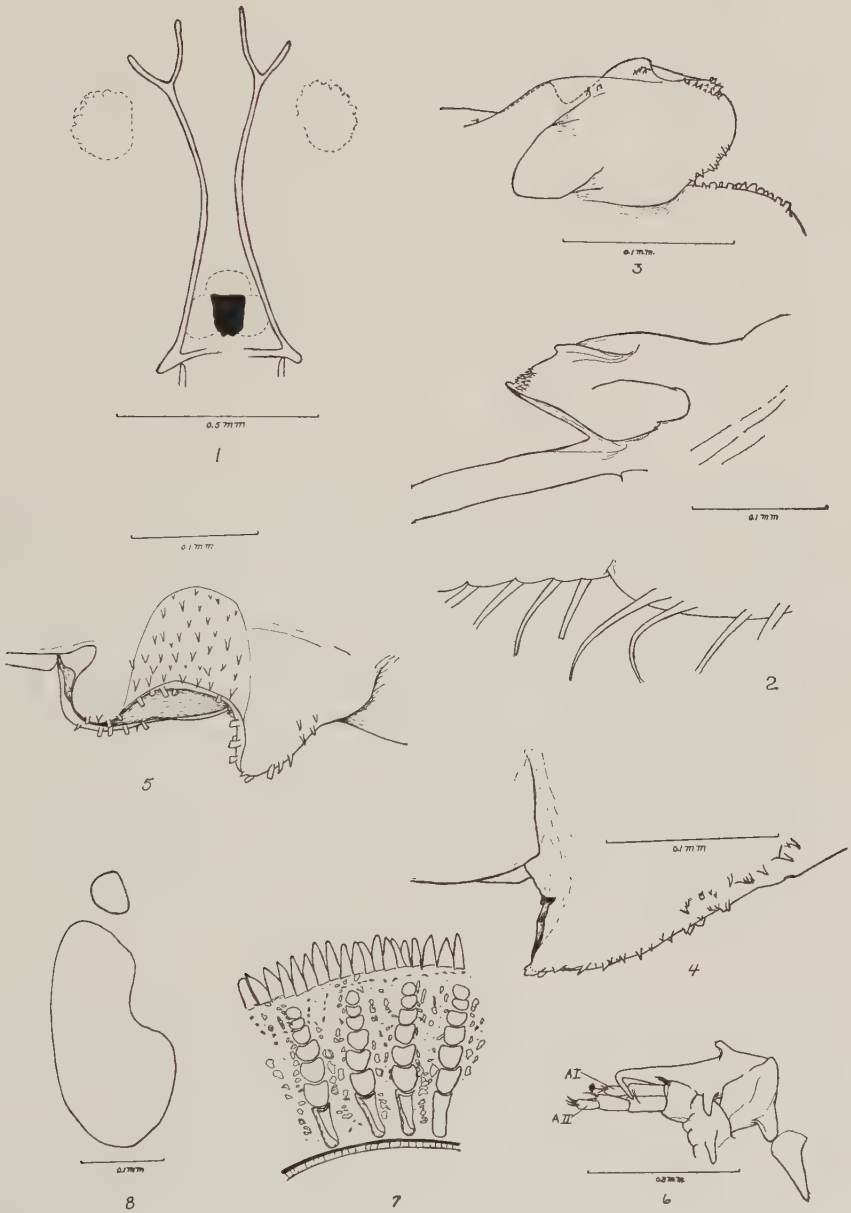
EXPLANATION OF PLATE

Fig. 1. Dorsal ribs of *A. trilineatus*.
Fig. 2. Accessory appendage of fourth legs on male.
Fig. 3. Similar appendage from *A.* foliaceous.
Fig. 4. Accessory appendage of second legs of male.
Fig. 5. Similar appendage on *A. trilineatus*.
Fig. 6. Antennae of *A. trilineatus*.
Fig. 7. Ribs of the sucking disc.
Fig. 8. Respiratory areas.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BOOK NOTICES

Nineteenth Century Eugenics

In this book (a partial autobiography) a successful national leader of mature years reviews his own boyhood in the Oneida Community, a communistic venture in New York state in the four decades that embraced the middle of the nineteenth century. The eugenicist of today finds much to praise in this communal effort. Selective mating was practiced through "complex marriage" and children were brought up, not by their parents, but in a series of carefully supervised and graded departments. A strong religious motive pervaded this group and proved both the bond of early union and the basis of later dissention. Outside pressure completed the schism in the early 1880's. Much of this book treats of routine narrative that might be written of the life of any boy up to sixteen years, the story of the Community being interwoven into this narrative. This communal project was noble effort of a sincere people, an effort that deserved better success and wider emulation.—R. A. HEFNER.

My Father's House, an Oneida Boyhood, by Pierrepont Noyes. New York City, Farrar & Rinehart, 1937. $3.50.

Georg Wilhelm Steller

To most biologists the name of Steller is associated with Steller's jay and Steller's sea cow. It is thus a revelation to learn that this German naturalist in the service of Russia 200 years ago was a physician and a botanist and made his famous voyage to Alaska as a mineralogist with Bering's expedition in 1741. The harrowing tale of this expedition by sail in Arctic waters is best summarized by the fact that disease, mainly scurvy, claimed the lives of 31 men from a total of 78 in the exploring party and crew, Bering himself being one of the victims. Before and after the Alaskan expedition, Steller made natural history surveys in eastern Siberia, around Lake Baikal, the Kamtchatka peninsula, and along the great river courses to the North. He made long sledge journeys in the rigorous winters, handicapped less by climate than by the suspicions and intrigues of old Russia in the troublesome period that followed Peter the Great. Suspected of treason, Steller was arrested in Russia, transported to Siberia, acquitted, and died of a fever at the age of 36 while returning to Russia.

The data collected for this book was accumulated by the author over a period of more than 50 years. The book is more than an exhaustive biography of a great naturalist; it is a model of meticulous detail in biographical writing.

—R. A. HEFNER.

Georg Wilhelm Steller, the Pioneer of Alaskan Natural History, by Leonard Stejneger. 623 pp. Cambridge, Harvard University Press, 1936. $6.00.

Man and His World

This book is the successor to "The Nature of the World and of Man." It is extensively rewritten and brought up to date. The authors of the various chapters are professors (in one case a former professor) at the University of Chicago. The arrangement and material are improved over the former book, and the new volume seems admirably adapted to an orientation course. Certainly the material contained therein is basic and fundamental to a well-rounded education. Some of the chapters are extremely stimulating and fairly self-explanatory; others, such as the one on particles and waves, seem beyond the freshman level and will require much "teaching." On the whole the book is a fine and successful attempt to provide a broad overview of man and his world.—L. H. S.

The World and Man as Science Sees Them, edited by Forest Ray Moulton. xix+533 pages. Chicago, The University of Chicago Press, 1937. Text Edition, $3.00.

SOME CLADONIAE FROM SOUTHWESTERN OHIO

Cladoniae from Clermont, Brown, and Adams Counties

M. FULFORD,
University of Cincinnati

At the present time there are few published records for species of Cladonia in southwestern Ohio. Dr. Bruce Fink's many papers on Cladonia species include general distribution data rather than locality records, so that while he no doubt studied plants from the southwestern part of the state his published reports do not include such. Mr. Thomas G. Lea[1] listed a number of species but his records are from Hamilton County (Cincinnati) or Northern Kentucky and are not included in this report.

The present paper includes collections from Clermont, Brown and Adams Counties. They are east of Hamilton County (Cincinnati) in the order named, and all of them border on the Ohio River. Except for the hilly areas along the Ohio and its tributaries, Clermont and Brown Counties are mostly made up of poorly drained upland flats of glacial till, where pin oak, swamp white oak, and sweet gum are conspicuous trees. (Much of the area has been cleared and is now under cultivation.) Most of Adams County is unglaciated. It is primarily an area of high hills and narrow valleys. Limestones and shales are the principle underlying rocks though sandstone is occasionally found at the tops of some of the higher ridges. The forests are prevailingly of the deciduous type though occasional pine areas occur.

The Cladonias are most abundant in old abandoned fields in both Clermont and Brown Counties; in Adams County they occur in great abundance along old wagon roads, in open pine woods, and on ridge tops, as well as in the grassy meadows.

The writer wishes to express her sincere appreciation in acknowledgment of the kindness of Dr. A. W. Evans, of Yale University, who has determined the material, and given helpful criticism in the preparation of this paper. Some of the speci-

[1]Lea, Thos. G. Catalogue of the plants, native and naturalized, collected in the vicinity of Cincinnati, Ohio, during the years 1834–1844, by Thos. G. Lea, Philadelphia, 1849.

mens were sent by Dr. Evans to Dr. Sandstede, of Bad Zwischenahan, Oldenburg, and his determinations and comments are noted under the specimens in question.

The specimens in the list which follows are arranged according to the classification of Vainio[2] which has been adopted by most of the recent writers on Cladonia. Unless otherwise noted the specimens were collected by the writer. The specimens are in the herbarium of Yale University, with a duplicate set in the herbarium of the University of Cincinnati.

Subgenus **Cladina**

Cladonia rangiferina (L.) Web. On earth in fields. The species is rare in the southwestern past of the state, and most of the specimens which have been locally referred to this species, are found, on examination, to be *C. tenuis*, which is very common. The only known station contains four or five clumps six to eight inches in diameter. Brown Co.: Quinn School near Vera Cruz.

Cladonia tenuis (Floerke) Harm. On soil in open woods and fields. This is the only abundant species of the subgenus Cladina in southwestern Ohio. Adams Co.: Beaver Pond; Lynx. Brown Co.: Quinn School near Vera Cruz; Vera Cruz (Miss Braun).

Cladonia tenuis f. *setigera* Sandst. Adams Co.: Mineral Springs. Brown Co.: Quinn School near Vera Cruz. Clermont Co.: Nicholsville (Miss Braun).

Subgenus **Pycnothelia**

Cladonia papillaria (Ehrh.) Hoffm. On clay soil, banks, hillsides, and open fields. Not common. The species is represented by the three forms listed below.

Cladonia papillaria f. *molariformis* (Hoffm.) Schaer. Adams Co.: near Beaver Pond; Mineral Springs. Brown Co.: Quinn School near Vera Cruz (Dowd).

Cladonia papillaria f. *papillosa* Fr. Adams Co.: Mineral Springs.

Cladonia papillaria f. *prolifera* (Wallr.) Schaer. Adams Co.: Beaver Pond.

Subgenus **Cenomyce**

Section 1. **Cocciferae**

Subsection 1. **Subglaucescentes**

Cladonia bacillaris (Ach.) Nyl. On decaying logs and stumps. Not frequent. Adams Co.: Beaver Pond; Mineral Springs. Brown Co.: Quinn School near Vera Cruz.

Cladonia didyma (Fée) Vainio. On dry, decaying logs. Not

[2]Vainio, E. Monographia *Cladoniarum universalis*. Pars prima. Acta Soc. Fauna et Flora Fennica 4: 1–510. 1887. Pars secunda. Ibid. 10: 1–499. 1894. Pars tertia. Ibid. 14: 1–268. 1897.

common. Adams Co.: Mineral Springs. Dr. Evans says of this specimen that it is probably the form *subacuta* but that it is not distinctive.

Cladonia didyma f. *squamulosa* Robbins. Adams Co.: Mineral Springs.

Subsection 2. **Stramineo-flavidae**

Cladonia cristatella Tuck. On old wood, bases of trees, and soil in fields and open woods. Widely distributed. Adams Co.: Beaver Pond. Brown Co.: Quinn School near Vera Cruz.

Cladonia cristatella f. *Beauvoisii* (Del.) Vainio. Adams Co.: Beaver Pond; Lynx; Mineral Springs. Brown Co.: Quinn School near Vera Cruz; Vera Cruz (Miss Braun).

Cladonia cristatella f. *vestita* Tuck. Adams Co.: Beaver Pond; Lynx; Mineral Springs. Brown Co.: Quinn School near Vera Cruz; Vera Cruz (Miss Braun).

Section 2. **Ochrophaeae**

Subsection 1. **Unciales**

Cladonia uncialis (L.) Web. On soil in open hillside woods. Rare. Clermont Co.: Nicholsville (Miss Braun).

Cladonia caroliniana (Schwein.) Tuck. On earth in open woods in hilly localities. Rare. The species is represented only by one form.

Cladonia caroliniana f. *dilatata* Evans. Adams Co.: Mineral Springs.

Subsection 2. **Chasmariae**

Group 1. **Microphyllae**

Cladonia furcata (Huds.) Schrad. On soil in fields and open woods, sometimes on rocks. The species and its forms are very common throughout the area. One variety and three forms have been collected. Brown Co.: Quinn School near Vera Cruz.

Cladonia furcata var. *racemosa* (Hoffm.) Floerke. Adams Co.: Beaver Pond; Mineral Springs; Lynx. Brown Co.: Quinn School near Vera Cruz. Clermont Co.: Milford.

Cladonia furcata var. *racemosa* f. *corymbosa* (Ach.) Vainio. Adams Co.: Bundle Run (Miss Braun); Mineral Springs; Lynx. Brown Co.: Quinn School near Vera Cruz; Vera Cruz (Miss Braun).

Cladonia furcata var. *racemosa* f. *squamulifera* Sandst. Adams Co.: Beaver Pond. Brown Co.: Quinn School near Vera Cruz; Vera Cruz (Miss Braun). Clermont Co.: Cabin Run (Miss Braun).

Cladonia squamosa (Scop.) Hoffm. On soil in open woods. The species is not abundant in the area. Clermont Co.: Nicholsville (Miss Braun).

Cladonia squamosa f. *levicorticata* Sandst. Adams Co.: Mineral Springs.

Cladonia delicata (Ehrh.) Floerke. On decayed oak stumps and logs. Common locally. The specimens all belong to one form.

Cladonia delicata f. *quercina* (Pers.) Vainio. Adams Co.: Beaver Pond; Mineral Springs.

Cladonia caespiticia (Pers.) Floerke. On soil, on banks, in fields, and in open woods. Not uncommon locally. Adams Co.: Beaver Pond; Mineral Springs.

Group 2. **Megaphyllae**

Cladonia apodocarpa Robbins. On earth in abandoned fields. Frequent. Adams Co.: Beaver Pond; Lynx. Brown Co.: Quinn School nera Vera Cruz.

Subsection 3. **Clausae**

Group 1. **Podostelides**

Cladonia mitrula Tuck. On soil in fields and on banks, sometimes over tree roots. Very common. Our specimens represent two forms.

Cladonia mitrula f. *imbricatula* (Nyl.) Vainio. Adams Co.: Beaver Pond; Lynx. Clermont Co.: Bethel (Twichel); near Nicholsville.

Cladonia mitrula f. *pallida* Robbins. Brown Co.: Vera Cruz (Miss Braun).

Cladonia clavulifera Vainio. On earth in abandoned fields. Not common. Brown Co.: Quinn School near Vera Cruz. Determined by Dr. Sandstede. Clermont Co.: Nicholsville (Miss Braun).

Cladonia clavulifera f. *nudicaulis* Evans. Brown Co.: Quinn School near Vera Cruz.

Cladonia subcariosa Nyl. On earth in fields, on roadside banks, and in open woods. Very abundant. Adams Co.: Beaver Pond. Clermont Co.: Nicholsville (Miss Braun).

Cladonia subcariosa f. *evoluta* Vainio. Adams Co.: Beaver Pond. Brown Co.: Quinn School near Vera Cruz (Miss Braun).

Cladonia subcariosa f. *squamulosa* Robbins. Adams Co.: Beaver Pond. Brown Co.: Quinn School near Vera Cruz; Vera Cruz (Miss Braun).

Cladonia brevis Sandst. On soil bank. The specimen is represented by *thallus* only. It was determined by Dr. Sandstede. Adams Co.: Beaver Pond.

Group 2. **Thallostelides**

Cladonia gracilis (L.) Willd. The species is rare in this region and is represented only by a variety and a form.

Cladonia gracilis var. *dilatata* (Hoffm.) Vainio. Brown Co.: Quinn School near Vera Cruz.

Cladonia gracilis var. *dilatata* f. *dilacerata* (Floerke) Vainio. Adams Co.: Beaver Pond.

Cladonia verticillata (Hoffm.) Schaer. On soil on banks and in fields. Very abundant. Brown Co.: Quinn School near Vera Cruz.

Cladonia verticillata f. *apoticta* (Ach.) Vainio. Adams Co.: Beaver Pond. Brown Co.: Vera Cruz (Miss Braun). Clermont Co.: Nicholsville (Miss Braun).

Cladonia verticillata f. *evoluta* (Th. Fr.) Stein. Adams Co.: Beaver Pond; Lynx. Brown Co.: Quinn School near Vera Cruz; Vera Cruz (Miss Braun). Clermont Co.: Bethel (Twichel).

Cladonia verticillata f. *phyllocephala* (Flot.) Oliv. Adams Co.: Beaver Pond; Lynx. Brown Co.: Vera Cruz (Miss Braun).

Cladonia pyxidata (L.) Hoffm. On soil, hillside under red cedar. Rare. The species is represented by one variety.

Cladonia pyxidata var. *neglecta* (Floerke) Mass. Clermont Co.: Nicholsville (Miss Braun).

Cladonia chlorophaea (Floerke) Spreng. On soil in fields, open woods, and banks, sometimes on the bases of trees. Common. Brown Co.: Quinn School near Vera Cruz.

Cladonia chlorophaea var. *intermedia* Sandst. Adams Co.: Lynx. The specimen was determined by Dr. Sandstede.

Cladonia grayi Merrill. On soil in fields and open woods. Frequent. Most of the specimens have been verified by Dr. Sandstede. Adams Co.: Mineral Springs; Lynx. Brown Co.: Vera Cruz (Miss Braun). Clermont Co.: Nicholsville (Miss Braun).

Cladonia fimbriata (L.) Fr. On soil in abandoned field. Rare. Brown Co.: Quinn School near Vera Cruz.

Cladonia nemoxyna (Ach.) Nyl. On soil in abandoned field. Rare. Dr. Sandstede has given a provisional name *C. subnemoxyna* to all those forms originally included in *C. nemoxyna* which show a negative reaction with paraphenylendiamin. This negative reaction is characteristic of our specimen. The restricted *C. nemoxyna* always gives a positive reaction. Dr. Evans says that apparently the latter is much more common in North America. Brown Co.: Quinn School near Vera Cruz.

Cladonia coniocraea (Floerke) Spreng. On soil in fields and open woods. Common. Adams Co.: Mineral Springs; Beaver Pond.

Cladonia coniocrea f. *ceratodes* (Floerke) Dalla Torre & Sarnth. Adams Co.: Beaver Pond; Lynx; Mineral Springs. Brown Co.: Vera Cruz (Miss Braun). Some of the specimens have been examined by Dr. Sandstede.

Cladonia coniocrea f. *robustior* (Harm.) Sandst. Adams Co.: Beaver Pond; Mineral Springs. Both of these determinations were verified by Dr. Sandstede.

Cladonia coniocrea f. *truncata* (Floerke) Dalla Torre & Sarnth. Adams Co.: Beaver Pond; Mineral Springs; Lynx. Brown Co.: Vera Cruz (Miss Braun).

Cladonia borbonica (Del.) Nyl. On logs, soil banks and thin soil over rocks. Frequent. Brown Co.: Quinn School near Vera Cruz.

Cladonia borbonica f. cylindrica Evans. Adams Co.: Beaver Pond. Brown Co.: Quinn School near Vera Cruz; Vera Cruz (Miss Braun). Clermont Co.: Branch Hill (Cooke); Milford.

Cladonia pityrea (Floerke) Fr. On soil and old wood. Not common. The species is represented by one variation.

Cladonia pityrea var. *Zwackhii* f. *subacuta* Vainio. Adams Co.: Mineral Springs. Brown Co.: Vera Cruz (Miss Braun).

Group 5. **Foliosae**

Cladonia strepsilis (Ach.) Vainio. On soil in fields and open woods. Frequent. Brown Co.: Quinn School near Vera Cruz.

Cladonia strepsilis f. *coralloidea* (Ach.) Vainio. Adams Co.: Beaver Pond (Fahnestock). Brown Co.: Quinn School near Vera Cruz.

Group 4. **Ochroleucae**

Cladonia piedmontensis Merrill. On soil in fields and open woods. Frequent. The species is represented locally by three forms.

Cladonia piedmontensis f. *lepidifera* (Vainio) Robbins. Brown Co.: Quinn School near Vera Cruz. Clermont Co.: Nicholsville (Miss Braun).

Cladonia piedmontensis f. *squamulosa* Robbins. Adams Co.: Beaver Pond. Brown Co.: Vera Cruz (Miss Braun).

Cladonia piedmontensis f. *squamosissima* Robbins. Brown Co.: Vera Cruz (Miss Braun).

Twins

The eagerly awaited comprehensive report of Professor Newman's studies of twins is at last at hand, and a very fine treatise it is. Newman has enlisted the aid of a psychologist and of a statistician in evaluating the data, and the resulting book is the co-ordinated report of the three men. The data presented include careful physical and mental measurements of fifty pairs of identical twins reared together, fifty pairs of like-sexed fraternal twins reared together, and nineteen pairs (twenty including Muller's case) of identical twins reared apart. The data are presented in full, with complete statistical analyses. The authors' interpretations are carefully and dispassionately presented, with clear distinctions between factual and theoretical conclusions. A strong case is made for pre-natal differences in the environments of identical twins, involving unequal blood exchange between twin fetuses, and the asymmetry mechanism, and resulting in certain differences between identical twins reared together. The authors agree that some characteristics are more susceptible to environmental differences than are others; also that as more research becomes available on the complex of genetic and environmental factors that interact in the development of individuals, more and more problems appear, none of which has an easy or general solution. This book belongs on the "must" list of every biologist and psychologist.—L. H. S.

Twins: A Study of Heredity and Environment, by H. H. Newman, F. N. Freeman, and K. J. Holzinger. xvi+369 pp. Chicago, University of Chicago Press, 1937. $4.00.

Haploids and Polyploids

This pamphlet contains a concise summary of the occurrence of haploids and polyploids in flowering plants. Polyploidy in somatic cells, polyploid gametes and polyploidy as the result of hybridization are treated separately. The plants in which polyploidy is known to occur are listed, and the causes, both natural and artificial, are briefly discussed. There is also an extensive bibliography of the literature on haploids and polyploids. It is a valuable reference for anyone interested in polyploidy.—D. C. Rife.

The Experimental Production of Haploids and Polyploids. 27 pp. Imperial Bureau of Plant Genetics, School of Agriculture, Cambridge, England, 1936.

NEW SOUTHWESTERN BUPRESTIDAE AND CERAMBYCIDAE WITH NOTES

JOSEF N. KNULL,

The Ohio State University

Acmaeodera gibbula Lec. and **A. alicia** Fall.

Reared from the dead branches of palo verde (*Cercidium torreyanum* Sarg.) collected at Tucson, Ariz.

Acmaeodera yumae n. sp.

Robust, depressed; head, pronotum, ventral surface and legs bronze, elytra yellow, each elytron margined with a narrow dark border on all sides, an irregular dark stripe extending from base, over umbone, to near apex; head, pronotum, ventral surface and legs clothed with long pubescence which partly obscures the surface.

Head convex, no trace of median depression; surface coarsely punctured; eyes large, finely granulate; antennae serrate beginning with the fifth joint.

Pronotum wider than long, widest back of middle, wider at base than at apex, sides broadly rounded from base to apex; lateral margin not visible from above; anterior margin sinuate, median lobe broadly rounded; basal margin truncate; disk convex, a shallow depression in front of region of scutellum; surface coarsely confluently punctured.

Elytra about same width as pronotum; sides nearly parallel at base, constricted in front of middle, broadly rounded to obtusely rounded apices; side margins serrulate back of middle; disk convex, umbone prominent; surface with coarsely punctured striae arranged in pairs, every other interval wider, punctures of intervals fine, a long fine hair arising from each interval puncture.

Abdomen beneath finely punctured, last ventral segment with a rounded subapical ridge. Front margin of prosternum retracted, sides not reaching the front angles, a dentiform prominence on each side of middle.

Length, 11 mm.; width, 3.5 mm.

Holotype labeled Yuma, Ariz., April 11, 1933, E. D. Ball, collector, in the collection of the writer.

According to Fall's key[1] this species would come in the Sinuata group next to *A. lanata* Horn. The dense vestiture of the ventral surface together with the markings of the elytra will serve to separate this species from the closely related forms.

Acmaeodera constricticollis n. sp.

Form robust; elongate, head, pronotum and ventral surface bronze, elytra yellow with numerous irregular small dark spots.

Head convex, no trace of median depression, surface with large

[1]H. C. Fall. Jour. N. Y. Ent. Soc., VIII, pp. 1–37. 1899.

shallow punctures, densely clothed with long white pubescence; eyes large, finely granulate; antennae serrate beginning with the fifth joint.

Pronotum wider than long, widest back of middle, wider at base than at apex; sides in front oblique to constricted apex, broadly rounded to basal constriction; lateral margin not visible from above; anterior margin sinuate, median lobe prominent; basal margin broadly emarginate; disk convex, slight trace of median depression; surface with punctures coarse in front of scutellum, large shallow punctures in front and toward sides, clothed with long pubescence, white scales at sides.

Elytra broader than widest part of pronotum; side margins rounded in front to constriction in front of middle, then broadly rounded to obtusely rounded apices; lateral margins serrulate back of middle; disk convex, umbone prominent; surface with strial punctures confluent, punctures of interspaces small, a short, recumbent hair arising from each interspace puncture.

Ventral surface and legs clothed with white scales which obscure most of the sculpture. Abdomen beneath densely punctured, last ventral segment without a subapical plate. Front margin of prosternum straight, sides not reaching the front angles.

Length, 8.8 mm.; width, 2.8 mm.

Holotype labeled Phoenix, Ariz., July 15, 1936, E. D. Ball, collector, in the collection of the writer.

This species belongs to the Truncate group and would come next to *A. cribricollis* Horn. However, the form of the prothorax will separate the two.

Tyndaris balli n. sp.

(Fig. 1)

Female—Form robust; head, thorax and ventral surface bronze, each elytron with edges piceous varying to dark brown with a bronze luster, inner portion which occupies most of the elytra yellow.

Head convex, no trace of median depression; surface reticulate, clothed with scale-like recumbent pubescence; eyes finely granulate; antennae reaching to about middle of pronotum when laid along side margin, serrate from the fourth joint.

Pronotum wider than long, widest back of middle, narrower at apex than at base; disk moderately convex, a deep depression on each side at base, base longitudinally rugose along margin; lateral margin inferior in front; sides broadly rounded from base to apex; anterior margin sinuate, slightly lobed; basal margin nearly straight; surface reticulate clothed with broad spatulate scales. Scutellum triangular.

Elytra at base not as wide as widest part of pronotum, metasternal episterna covered by elytra; sides constricted at base, and in front of middle, broadly rounded posteriorly to rounded apices, side margins serrulate from about middle; disk flattened, umbone prominent; striate, striae coarsely punctured, interspaces containing spatulate recumbent pubescence.

Abdomen densely clothed with spatulate white scales, last abdominal segment rounded, not spiniform.

Tarsi slender, not cordiform, claws each with a blunt basal tooth.

Length, 5.3 mm.; width, 2.3 mm.

Male—Differs from female by the longer antennae and broader outer joints.

Described from specimens collected at Congress Junction, Ariz., June 19, 1935, by Dr. E. D. Ball, in whose honor the species is named. Holotype female, allotype and paratypes in the writer's collection. Paratypes in collection of the University of Tucson and The Ohio State University.

This species agrees with the genus *Tyndaris* better than with *Paratyndaris* although the form of the tarsi could apply to the latter genus. I have placed it provisionally in the former genus.

Hesperorhipis mirabilis n. sp.

(Fig. 2)

Ventral surface dark blue becoming more brilliant at ventral portion of prothorax, head and pronotum brilliant metallic green, each elytron with a large basal triangular metallic green area extending along suture, a transverse curved white band extending from costal margin to suture and narrowly extending along suture, rest of elytra dark blue.

Male—Head convex, slight indication of median depression; surface asperate on front, reticulate on vertex; eyes small, finely granulate; antennae dull testaceous, extending about one-third the length of the elytra when laid along the side of the pronotum, flabellate, quite similar to that of *Xenorhipis brendeli* Lec. figured by Horn,[2] rami beginning at the third joint; last joint of maxillary palpus ovate, apex rounded.

Pronotum wider than long; anterior margin sinuate, median lobe broadly rounded; basal margin slightly sinuate at middle of each elytron; disk convex, without depressions, or raised areas; lateral margin inferior in front, present in basal third only; sides nearly parallel in middle, acutely rounded in front and broadly rounded in back; surface reticulate. Scutellum dark blue, granulate.

Elytra with base not as wide as base of pronotum, not covering the abdomen but extending to first abdominal segment only, twice as long as wide; sides nearly parallel in front, constricted back of middle, broadly rounded posteriorly to acutely rounded apices, sutural margin sinuate back of middle; surface rugose, rugae less evident in white area; under wings visible, tips extending to beyond end of abdomen.

Abdomen beneath asperately punctate; sides of metasternum with a large hairy depression, or excavation. Basal joint of hind tarsus equal in length to the three following joints.

Length, 3.5 mm.; width, 1.2 mm.

Described from male specimens taken on the foliage of one of the cat's claws (*Acacia* sp.) in the Gila Mountains, Ariz., on July 7 to 9, 1936, by the author. Holotype and paratypes in the writer's collection.

This species is closely related to *H. albofasciatus* Fall. However, the excavation on the side of the metasternum will serve to separate it from his species. Professor Fall informs me that the type is lacking this depression.

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[2]A. H. Horn. Trans. Amer. Ent. Soc., 10, p. 165. 1882.

Agrilus cercidii n. sp.

Male—Form small, narrow, elongate, subcylindrical, shining, piceous; each elytron with three patches of white pubescence along suture, one in basal depression, an elongate patch at middle and one on apical third.

Head strongly convex with greenish tinge, without median depression; surface finely granulose, pubescence sparse; antennae short, reaching to about middle of pronotum when laid along side margin, serrate from the fifth joint, outer joints wider than long.

Pronotum slightly wider than long, narrower at base than at apex, side margins feebly arcuate; when viewed from the side the marginal and submarginal carinae are separated for their entire length; anterior margin sinuate, median lobe broadly rounded; basal margin strongly emarginate at middle of each elytron, disk convex, without depressions, prehumeral carinae lacking; surface obsoletely granulose, obliquely rugose, the rugae widely separated, pubescence sparse. Scutellum triangular, without transverse carina.

Elytra at base wider than base of pronotum; side margins nearly parallel to middle, constricted back of middle, obliquely rounded to rounded, serrulate apices; disk moderately convex; sutural margin elevated posteriorly, shallow basal depressions, in addition, each elytron with an elongate depression at middle and one in apical third, depressions containing dense recumbent white pubescence; surface irregularly rugose, pubescence well spaced, short.

Abdomen beneath obsoletely reticulate, clothed with short, widely separated pubescence, suture between first two ventrals not indicated at sides; median line of pubescence short, inconspicuous; first two ventral segments unmodified. Prosternal lobe truncate with slight emargination at middle; prosternal process parallel to back of coxal cavities, then attenuate to apex. Posterior coxae with posterior margin strongly sinuate, the exterior angle not prolonged, outer portion of plate densely pubescent. Tibiae slender, anterior pair mucronate on inner side at apex. Tarsal claws similar on all feet, cleft, inner tooth broad, much shorter than outer one and not turned inward.

Length, 2.3 mm.; width, .6 mm.

Female—Differs from the male in having front of head cupreous, tibiae not mucronate, median pubescence of ventral surface not longer than others.

Described from one pair of adults collected from the foliage of palo verde (*Cercidium torreyanum* Sarg.) in Sabino Canyon, near Tucson, Arizona, August 10, 1936, by the author. Holotype male and allotype in writer's collection.

According to Fisher's key,[3] this species would run to *A. abjectus* Horn. However, it more closely resembles *A. abstersus* Horn from which it differs in male genitalia and by the presence of the elytral spots. The genitalia resemble those of *A. costipennis* Fisher, as figured by him.[3]

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[3]W. S. Fisher. U. S. Nat. Mus. Bul. 145, pp. 1–349. 1928.

Agrilus cavifrons Waterh.

Specimens which tally with the description and figure of this species were taken on the foliage of desert hackberry (*Celtis pallida* Torr.) in Sabino Canyon near Tucson, Ariz., from August 8 to 14, by the author.

Agrilus exhuachucae n. sp.

Male—Form narrow, elongate, subcylindrical, piceous; head with front bronzy green, vertex cupreous; pronotum aeneous; each elytron with a bright cupreous area covering basal fifth and extending along costal margin to apex.

Head convex, a slight trace of median depression; surface with large light punctures, pubescence sparse, obscure; antennae short, not reaching to middle of pronotum when laid along side margin, serrate from the fifth joint, outer joints wider than long.

Pronotum wider than long, widest in apical fourth, much narrower at base than apex; side margins broadly arcuate in front, oblique posteriorly, sinuate at base; when viewed from the side the marginal and submarginal carinae widely separated in front but joined on basal fifth; anterior margin sinuate, median lobe strongly rounded; basal margin emarginate at middle of each elytron; disk convex, a short median basal depression in front of scutellum, lateral depressions feeble, prehumeral carinae prominent; surface finely transversely rugose, finely punctate between rugae, each puncture bearing an inconspicuous hair. Scutellum granulate, transversely carinate.

Elytra wider than base of pronotum; side margins sinuate in front, strongly constricted at middle, broadly rounded to rounded crenulate apices; disk moderately convex, sutural margin elevated posteriorly; basal depressions deep, a faint longitudinal carina between humeri and lateral margin; surface imbricately granulose, pubescence short, well spaced, inconspicuous.

Abdomen beneath shining, reticulate, clothed with short widely separated pubescence which is longer on median line of first two segments, suture between first two ventrals well indicated at sides, first two ventrals unmodified. Prosternal lobe broadly rounded, no indication of emargination at middle; prosternal process expanded back of front coxal cavities. Posterior coxae with the posterior margin strongly sinuate, the exterior angle slightly prolonged. Tibiae slender, anterior pair mucronate on inner side at apex. Tarsal claws nearly similar on all feet, cleft, inner tooth broad, much shorter than outer one and not turned inward.

Length, 4.5 mm.; width, 1 mm.

Female—Differs from the male in having front of head aeneous, tibiae not mucronate, median line of pubescence of ventral surface not longer than others.

Described from a pair of adults collected from the foliage of oak (*Quercus* sp.) in the Huachuca Mountains, Ariz., July 21, 1936, by the writer. Holotype male and allotype in author's collection.

According to Fisher's key[3] this species would run to *A. abditus* Horn. The color markings will separate it from its allies. Super-

ficially it resembles *A. duncani* Knull; however, the elytral apices of the two species are quite distinct.

Methia evaniformis n. sp.

(Fig. 3)

Male—Size and form of *Molorchus bimaculatus* Say; robust, piceous, area bordering eyes and antennae brunneus, elytra ochraceous.

Head convex, front perpendicular, deeply channeled between antennae; eyes deeply emarginate, but not divided, lower lobe much larger than upper one, coarsely granulate, widely separated on vertex; surface coarsely punctured, punctures contiguous, pubescence fine; antennae about twice as long as entire insect, fifth joint extending beyond tips of elytra, scape stout, second joint wider than long, third joint much longer than scape, joints four to eleven inclusive, gradually diminishing in length, scape coarsely punctured, other joints finely punctured and densely pubescent, especially on outside.

Pronotum wider than long, widest in middle, narrower at base than at apex; sides broadly rounded from apical to basal constriction; disk convex; surface confluently coarsely punctured, a transverse callous area at base, densely clothed with long silky pubescence. Scutellum triangular, channeled.

Elytra as long as wide; wider than pronotum, widest just back of base; sides broadly rounded in front, sinuate in middle, apices obliquely truncate; suture strongly sinuate; disk convex, umbone prominent, surface densely finely punctured, punctures becoming confluent apically, pubescence short, fine; under wings extending beyond tip of abdomen.

Abdomen very short, not as long as metathorax. Metasternum densely coarsely punctured. Posterior legs very long, coxae large, femora shorter than tibiae, tibiae densely clothed with long piceous hairs.

Female—Differs from the male by somewhat shorter antennae and longer abdomen.

Length, 7.5 mm.; width, 1.8 mm.

Described from specimens collected in the Davis Mountains, July 3–August 22, and Chisos Mountains, Texas, July 9, 1936, by the author.

Holotype male labeled Davis Mountains, July third; allotype and paratypes in writer's collection.

This remarkable species which was collected from the dead branches of oak (*Quercus* sp.) was very active when it landed in the umbrella and had more the appearance of one of the *Evaniidae*.

The coarsely punctured pronotum, widely separated eyes, large metathorax and long posterior legs will serve to distinguish it from the other species in the genus.

Tragidion opacum n. sp.

Male—Size and form of *T. armatum* Lec., piceous, elytra brunneous, apices piceous.

Head opaque, irregularly punctured, front concave, eyes small, finely granulate; antennae much larger than elytra, eighth joint extending beyond apices when laid over dorsal surface, scape stout, second

joint slightly longer than wide, third joint longer than first two taken together, fourth shorter than third, joints five to ten gradually decreasing in length, terminal joint longest, joints four to ten slightly serrate.

Pronotum wider than long, widest in middle, narrower at apex than at base; sides oblique in front, an obtuse tubercle at middle; base constricted; disk convex, a median tubercle in front of scutellum, two on each side of anterior half and one on each side of posterior half; surface opaque, coarsely confluently punctured, each puncture bearing a recumbent piceous hair. Scutellum triangular, densely clothed with short pubescence.

Elytra at base wider than widest part of pronotum, sides nearly parallel at base, constricted at middle; parallel back of constriction, broadly rounded to emarginately truncate apices; disk convex, each elytron bearing three indistinct costae; surface densely coarsely punctured, each puncture bearing a recumbent piceous hair.

Abdomen beneath finely punctured, pubescence long. Hind tibiae bent backward at tip.

Length, 20.9 mm.; width, 5.8 mm.

Described from one male specimen in the collection of the author taken from the foliage of oak (*Quercus* sp.) in the Davis Mountains, Tex., July 4, 1936, by the writer.

This species resembles *T. armatum* Lec., but can be distinguished by the opaque, coarsely punctured pronotum, black elytral apices and color and placement of elytral pubescence.

Dorcaschema octovittata n. sp.

Male—Form and general appearance of a small specimen of *D. wildi* Uhler, background dark brown; legs and antennae lighter, body and legs clothed with recumbent white pubescence, body ornamented with fulvous stripes of the same texture pubescence.

Head with front flat, depressed between antennae, a blunt tubercle on inside of each antennal socket, a fine median line extending from pronotum to front; surface granulate in front, rugose on vertex, clothed with recumbent white pubescence marked with fulvous areas; antennae eleven jointed, fifth joint extending beyond tips of elytra, scape stout, second joint slightly longer than wide, scape and second joint asperate on upper side, third joint longer than fourth, sixth joint shorter than fifth, seventh joint longer than sixth, joints gradually increasing in length to tip, last joint longest, joints three to ten, inclusive, annulate at outer ends, white pubescence short, becoming very fine and inconspicuous on outer joints.

Pronotum longer than wide, widest back of middle; sides subparallel in front, constricted back of middle and expanded at base; anterior margin broadly emarginate; basal margin emarginate; disk convex, a vague transverse depression at base; surface transversely strigate, punctures large, irregularly placed, clothed with recumbent white pubescence, two fulvous stripes on side and a much broader one in middle, first lateral and middle stripe extending from anterior margin to basal depression, numerous long flying hairs near base. Scutellum triangular, clothed with white and fulvous pubescence.

Elytra much wider than prothorax; sides nearly parallel, broadly rounded posteriorly to rounded apices, disk convex; surface coarsely punctured, a patch of densely placed punctures back of middle on side of each elytron, clothed with recumbent white pubescence, each elytron with four fulvous stripes running the entire length.

Abdomen granulate, larger punctures well spaced, a long hair arising from each depression, clothed with white and fulvous pubescence. Legs clothed with dense white pubescence.

Length, 11.8 mm.; width, 3 mm.

Female—Differs from the male by the much shorter antennae and the smaller, less densely pubescent anterior tarsal joints.

Described from specimens taken from Mexican mulberry (*Morus celtidifolia* H. B. K.) in the Davis Mountains of Texas July 3 to 6, 1936, by the writer. The species breeds in the living trees. Holotype male, allotype and paratypes in writer's collection; paratypes in collection of the Ohio State University.

This species comes close to *D. wildi* Uhler but can be separated by the smaller size, the presence of four distinct yellow lines on each elytron and the much coarser elytral punctures. It lacks the two types of elytral punctures present in *D. wildi*.

Estola tigrina Skinn.

Reared from the dead branches of palo verde (*Cercidium torreyanum* Sarg.).

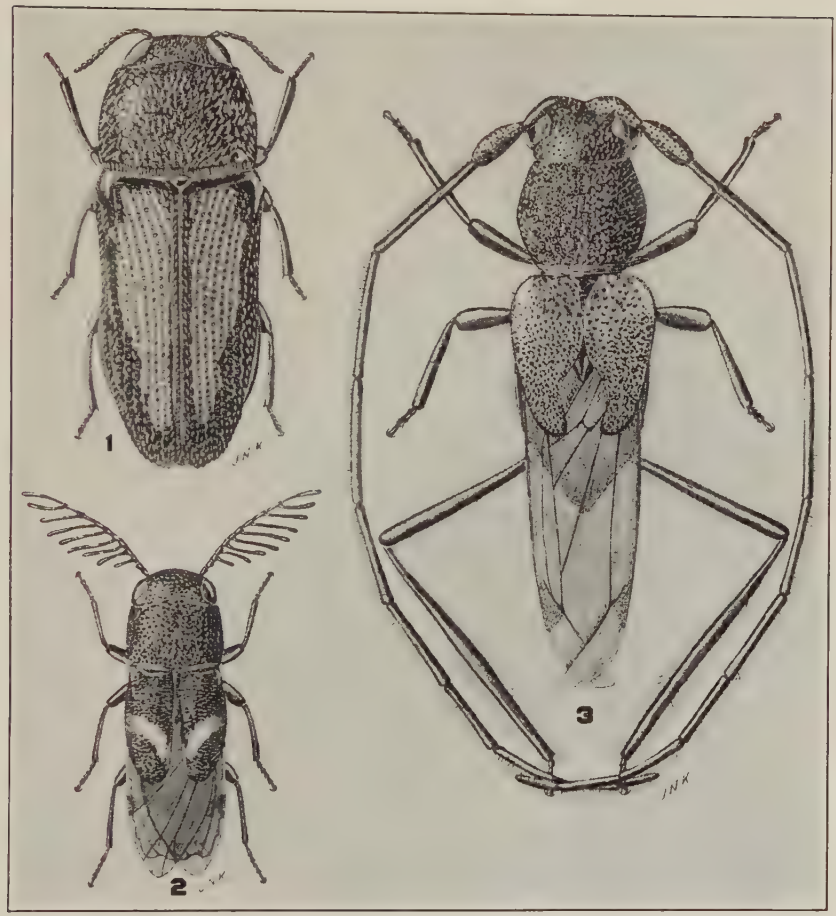

Fig. 1. *Tyndaris balli* n. sp.
Fig. 2. *Hesperorhipis mirabilis* n. sp.
Fig. 3. *Methia evaniformis* n. sp.

BOOK NOTICES

Entomological History

From his long and varied experience with entomology and entomologists Dr. Osborn has prepared and published this interesting account of the development of the science and of the persons responsible for its growth. He has dipped deep into his memories and withdrawn much of a personal nature that enlivens and enriches the book. Federal and state services, experiment stations, college departments, entomological societies and publications all form part of the historical pageant. Accounts of the outstanding insect collections are presented. The book is further personalized by the inclusion of a long series of short biographies of present-day entomologists, and an appendix of about 250 photographs.—L. H. S.

Fragments of Entomological History, by Herbert Osborn. vii+394 pp. Columbus, Ohio, published privately by the author, 1937.

The Life of Genius

Blaise Pascal receives honorable remembrance by all those who treat the history of science, for his arithmetical triangle, his principle of physics, and for many other contributions to mathematics and physics. In this new biography, however, the true proportions of his genius are disclosed in the description of his remarkable achievements in many other fields of endeavor. The exposition in both chronological and topical, this feature being permitted by a rather distinct metamorphosis in Pascal's life and in his thought. The author therefore describes, in turn, the Prodigy, the Inventor, the Convert, the Physicist, the Mathematician, the Man of the World, the Lover, the Mystic, the Penitent, the Polemist, the Philosopher, the Saint, and, in summary, the Man. Pascal, in his passionate search for the ultimate "certitude" in nature, turns radically from one intellectual sphere to the next, displaying his genius at each turn.

A large share of the book is devoted to the religious background of Pascal's period, which had great influence upon his life, even though it never completely dominated his own inductive method of logic. The book is written in a scholarly and entertaining style, and in a manner which invites much reflective thought. It is evidently the result of an exhaustive and critical study. References and controversial subjects are relegated to an appendix of notes, so as not to detract from the readability of the book.—C. W. COTTERMAN.

Pascal, The Life of Genius, by Morris Bishop. xi+398 pp. Baltimore, Williams and Wilkins Co., 1936. $3.50.

Metabolism

Doctor Holmes presents a rather frank appraisal of what we do not know about the metabolism of the individual tissues. He surveys with simplicity and brevity the general field of biochemical research, pointing out the most salient facts as well as some of the more evident blanks in our knowledge concerning the subject. The book is quite comprehensive in scope, taking up the difficult problem of organization within the cell through a consideration of the action of individual enzymes. Such topics as the metabolism of the liver, kidney and other tissues, the concept of oxidation-reduction potential, and the chemistry of the vitamins and hormones are discussed in details so fine and yet so fundamental that they make interesting and easy reading

This book should be of value to biologists, physiologists and others interested in the subject as a guide to the work that has been done and the work that needs to be done in biochemistry. Students of the life sciences should find it useful for gaining a quick acquaintance with, and a broad appreciation of the methods and present status of biochemical research. It is recommended as a supplementary text or as a reference for courses dealing with the activities of living tissues.

—HARRIET S. HYMAN.

The Metabolism of Living Tissues, by Eric Holmes. 235 pp. Cambridge, at the University Press; New York, The Macmillan Co., 1937. $2.25.

Breeding

This book is without doubt the most complete and thorough volume on animal breeding which has yet appeared. Modern genetics has contributed so much to the scientific knowledge of breeding that any adequate book on this subject must of necessity rest firmly on a genetic basis. This very fact brings the breeder up against much technical detail of genetics and biometry. Lush has done a remarkable job of combining technical and practical information into a readable and workable book. Certain unavoidable statistical concepts have been used, but so clearly are they developed, and so rationally introduced into the practical discussions that the breeder should have no difficulty in appreciating their importance. Animal husbandry departments which do not incorporate this book somewhere in their curriculum may fairly be said to be behind the times.

Following a discussion of the origin and domestication of farm animals, the general principles of genetics are briefly discussed in their relation to animal breeding. Then follow several chapters on breeding plans based on selection, on relationship, and on somatic likeness. Some general topics of interest to the breeder are taken up, followed by a chapter on sex and reproduction. The book closes with a general summary. It is not always easy to combine technical and practical information in workable form, but the result in this case is highly gratifying.—L. H. S.

Animal Breeding Plans, by Jay L. Lush. viii+350 pp. Ames, Iowa, the Collegiate Press, Inc., 1937.

Modern Alchemy

This small book contains in somewhat expanded form the subject matter of the Henry Sidgwick Memorial Lecture delivered in November, 1936. There are thirteen plates and eight figures which enhance the readability of this elementary thesis on nuclear physics. The older field of natural radioactive transformations is first reviewed. The discovery of the fundamental particles (neutron, deutron and positron) is clearly and simply presented. Special emphasis is placed upon the neutron. The methods and instruments for the production of high voltages and transmutations are briefly reviewed.

Since only the most outstanding points are touched upon, one may gain quickly from this book a very excellent perspective of the general field of nuclear physics and a glimmer of future possibilities.—M. L. Pool.

The Newer Alchemy, by Lord Rutherford. xii+67 pp. New York, the Macmillan Co., 1937. $1.50.

Educational Psychology

This book should be welcome both because the author is an authority on racial differences in mental abilities and because he has supplemented the conventional discussion of "original nature" in educational psychology texts by including a chapter on heredity. On neither count, however, is the level set by the book as a whole maintained. The materials of the chapters on motivation, learning, thinking, and achievement are well chosen and arranged. They reflect the author's fifteen years of teaching this subject matter.

With the term "selection" used to mean biased sampling, Dr. Garth's brief presentation of racial psychology concludes that, "racial differences in intelligence . . . are due to nurture and selection, and not to racial germ plasm." Since race problems are forever vexatious to students, it is regrettable that more of an answer than this is not afforded their questions. If biological differences are admitted as between individuals, it will be difficult to see why biological selection should not have been considered a possible factor as between racial groupings. With crucial data few indeed, the student could be better helped if it were pointed out that biological difference is not synonymous with biological superiority, that, taken together, marked cultural differences plus possible biological differences do not in fact produce more than small average differences between races, and that such differences as are found are slight compared to either individual differences or group differences within a race.

Galton's laws of ancestral inheritance and of filial regression might better have been omitted, especially since the student is left to suppose that the latter

law alone gave rise to the doctrine of the stability of the gene. He is also left to think little more of Johannsen's work than that it "verifies our statement that if we select two parental organisms, however closely related, their progeny will still show variation." The treatments given meiosis and linkage are vague. As a fundamental concept, the particulate nature of inheritance deserves emphasis in such a chapter, and to this end the re-telling of the tales concerning the Jukes and the Kallikaks might well be spared.—B. PRICE.

Educational Psychology, by Thomas R. Garth. xvi+319 pp. New York, Prentice-Hall, Inc., 1937. $2.50.

Sound

The most recent of a series of books on Sound by Professor Miller of the Case School of Applied Science, Cleveland, deals with his own researches in this field. Curiosity about the tone qualities of flutes made of different materials was the starting point of these studies, in the year 1900. In 1908 Miller devised the phonodeik, which he developed into the most faithful device for recording the wave form of sound which was available before the advent of electronic devices of the present day. Many phonodeik records are reproduced and discussed in this book, including tones of musical instruments and typical speech sounds.

By contrast, the second half of the book deals with sound waves from rifles of various sizes up to 14 inch guns. The object at first was to investigate the concussional wave from big guns as a possible cause of shell shock. Later, the facilities of the Sandy Hook Proving Ground were used in measuring the speed of sound and its variation near the guns. Results of these studies are presented for the first time in this book. Also included are photographs of bullets in flight and the accompanying sound waves, made by electric-spark photography.

This book is unusual in that it is a research report intended for a wider audience than a restricted group of specialists. Dealing with the outstanding findings of a long series of studies from a comprehensive viewpoint, without the exaggerated conciseness of a journal article, it may be read with pleasure by any one interested in sound.—HAROLD P. KNAUSS.

Sound Waves, Their Shape and Speed, by Dayton Clarence Miller. xii+164 pp. New York, The Macmillan Co., 1937. $2.75.

The Living World

"The Living World" was written to serve as a text for a cultural course in biology, nature study, or elementary ecology. The book is divided into four parts dealing with (1) the biological aspects of living things, (2) the kinds of animals and where they live, (3) plant study, and (4) suggestions for field study.

The book is essentially zoological, approximately only 100 pages being devoted to plants. It contains much material of general interest about animals. Chapters on color, sound, defenses, and life spans of animals add much interest, and are valuable even though they are debatable topics. The ecology is elementary, but complicated by avoiding standardized descriptive terms, for which in several instances, words of doubtful meaning are substituted. The portion devoted to botany contains a section on insect galls and their causative organisms. The practical suggestions for study are so basic to nature study that this section could be more useful if enlarged. A reference list of books and periodical literature at the end of most chapters will facilitate independent inquiry by the better students. Because of this feature, the text may serve as a reference book for students interested in field studies, even though they have had previous courses in biology.

Although this book is a departure from books on Natural History written in a popular style, it is not sufficiently divorced from the content and technique of the commonplace elementary biology text written from a purely morphological point of view. Frequently the text fails to adhere to factual evidence and statements are made without support. A *priori* logic combined with the idea of purposive adaptation is a detriment to correct thinking by students. Several errors involving misstatement of fact were noted.—CARL VENARD.

The Living World, by Samuel H. Williams. xxii+704 pp. New York, The Macmillan Co., 1937. $3.50.

Marconi

This is an accurate, interesting and most complete account of the life of Senatore Marconi, particularly during the period of the early development of wireless telegraphy in which Marconi played so important a part. The book is completely non-technical in nature, amounting to a detailed history of the most dramatic experiments of Marconi and the development of a practical system of what he chose to call wireless telegraphy, but now known generally as radio telegraphy. Quotations from the press (the author being Radio Editor of the New York Times) form a considerable part of the text and at times are a little tiresome, but lend a definite degree of completeness and authenticity. The author, being a former ship radio operator, dramatizes the first use of wireless telegraphy in saving life on shipboard in a vivid manner. Published shortly before Marconi's death, this book gives a historical account of the development of radio communication that clearly establishes Marconi's inventive genius and shows him in the role of practical inventor, business man, and scientist.—R. C. HIGGY.

Marconi: The Man and His Wireless, by Orin E. Dunlap, Jr. New York, The Macmillan Co., 1937. $3.50.

Uncertainties

Which of us has not at some time speculated about the beginning and the end of time, the boundaries of space, the possibility of an absolute post of observation and reference, simultaneity of events at different points, ultimate causality, freedom of thought and action? Here is a volume devoted to just such speculation, carefully thought out and thoroughly discussed. Not easy reading, it nevertheless holds the attention because it is so often a mirror of one's own unspoken thoughts. The warp of the discussion is the constantly changing scientific outlook, improving essentially as mathematical technics improve: the woof is man's difficulty in detaching himself from the cosmos which he is trying to describe and interpret. If one's questions are not all answered by the book, at least new lines of speculation will have been opened up.—L. H. S.

Aspects of Science, by Tobias Danzig. xi+285 pp. New York, The Macmillan Co., 1937. $3.00.

The Physiological Basis of Medical Practice

Physiology has long been known as the hand-maiden of medicine. The physiologist who has the responsibility of instructing medical students may rightly be expected to point out to his students the clinical applications of his science and to emphasize especially those aspects of the subject which are of value in the diagnosis and treatment of pathological conditions. Professors Best and Taylor, the eminent physiologists of the University of Toronto, have kept these facts constantly in mind in the preparation of their new book which has met with instantaneous and signal success. In spite of the fact that a generous proportion of the book is devoted to a consideration of the practical aspects and clinical applications of the subject, fundamental and classical physiology has by no means been neglected. Indeed the outstanding virtue of the book is its comprehensiveness. In it one can find the most recent developments in the pure science of physiology as well as a wealth of material which relates these developments to the practice of medicine. The book is written in a lucid and interesting style and its contents presented in logical sequence. It is divided into eight sections as follows: (1) the blood and lymph, (2) the circulation, (3) respiration, (4) the excretion of urine, (5) digestion, (6) metabolism and nutrition, (7) the ductless glands, and (8) the nervous system. A dogmatic attitude on controversial subjects has been studiously avoided. In such cases the important evidence on both sides is presented from an unbiased point of view. The book is much more than a test-book of medical physiology, it is an outstanding reference work for medical practitioners and for biologists in general.—F. A. HITCHCOCK.

The Physiological Basis of Medical Practice, by Charles Herbert Best and Norman Burke Taylor. xxiii+1684 pp. Baltimore, William Wood and Company, 1937. $10.00.

THE OHIO JOURNAL OF SCIENCE

VOL. XXXVII NOVEMBER, 1937 No. 6

FOREWORD

In 1933 the Ohio State Chapter of the Society of the Sigma Xi committed itself to the policy of sponsoring at biennial intervals series of lectures treating various aspects of some central scientific topic. At the completion of such a series of lectures it was the plan of the executive committee that it should be published and distributed at cost. Two such symposia have already been issued by the Chapter. In 1933 a Symposium on Metabolism was published and in 1935 the Chapter issued a Symposium on the Nucleus of the Atom. The success of these first two publications has been very gratifying and it is with a feeling of confidence as well as of pride that the Chapter presents the published version of this third series of lectures, A Symposium on Hormones.

The authors of the various papers included in this series are authorities in their several fields, and their researches constitute major contributions to our knowledge of the hormones. Naturally the treatment has not been exhaustive. The field is so broad and the physiology involved so complex that of necessity the several authors have selected some more or less limited aspect of the subject for elucidation. Furthermore limited time and facilities have made necessary the omission of certain of the hormones and therefore this volume contains no discussion of the hormones of the parathyroids, the thymus, or the pineal gland.

As was the case in the two preceding symposia, publication is made possible through the co-operation of the Ohio Journal of Science, and the executive committee of the Ohio State Chapter of the Society of the Sigma Xi wishes to express its appreciation to the editor and business manager of this Journal and to all others concerned for the splendid co-operation which made the

series of lectures so successful and which now makes their publication possible.

F. A. Hitchcock, *Secretary.*

Physiology Laboratories,
The Ohio State University.

Editor's Note

The Journal is again pleased to publish a Sigma Xi Symposium on a topic of current interest. The prompt publication of these lectures in symposium form is made possible by the financial assistance and the editorial co-operation of the Society of the Sigma Xi.—L. H. S.

THE GROWTH HORMONES FOUND IN PLANTS

GEORGE S. AVERY, JR.
Connecticut College

INTRODUCTION

Just what is a hormone? This question is the one which first comes to mind if one is not familiar with the subject. The term "*hormone*" is derived from a Greek work meaning "to arouse to activity." It was first suggested by Hardy and used by Starling in 1906 in reference to the substance *secretin*. In 1914 Starling defined a hormone as "any substance normally produced in the cells of some part of the body and carried to distant parts which it affects for the good of the body as a whole." This definition as applied to animal physiology is equally useful to the plant physiologist. Indeed, the naturally occurring plant hormones, as we now understand them in higher plants, are formed or stored in certain regions of the plant and moved to others where they become effective. The common characteristic of these compounds that lets us place them in the category of hormones is the fact that when present in very minute quantities, they bring about *growth* if other conditions such as food and water supply are not limiting. Their influence on growth is out of all proportion to the low concentration in which they occur.

The discoveries during the past 25 years of certain facts concerning the activity of plant growth hormones have given a clue to the long puzzling problem of plant responses to light and gravity, and through studies on these tropisms we have gained much new information regarding normal growth.

In short, the growth hormone theory is this: Assuming an adequate supply of food and water, growth will go on only if growth hormone, or *auxin* (as it is known also) is present. Without auxin, no growth takes place. The presence of auxin in minute quantities promotes cell stretching (elongation) in the direction of the long axis of an organ such as a petiole, or stem, hence auxin may be considered as promoting *polarized* growth—greater growth in length than in any other direction. For the present, at least, this statement must be limited to aerial portions, or shoots, of plants.

The relationship of cell division to the naturally occurring auxins is not sufficiently clear as yet to be discussed here, and so we shall assume for the present, at least, that these substances exercise their effect mainly on cell elongation.

All the earlier studies on auxin were made in connection with grass seedlings, mostly oats, *Avena sativa*. Other more recent work has been done on dicotyledonous seedlings such as lupine, broad bean, sunflower, etc. For the sake of clarifying the discussion that follows, diagrams of the oats and sunflower seedlings are given in Fig. 1. Growth hormones have been

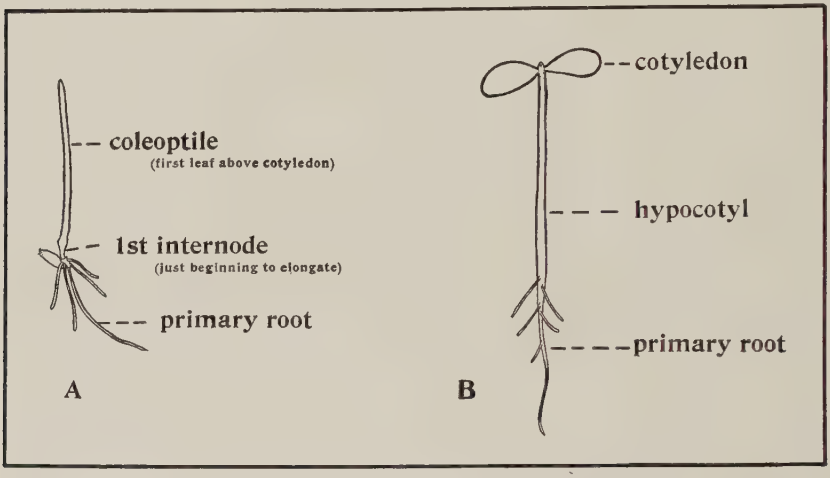

Fig. 1. A, seedling of *Avena sativa*. The coleoptile (cylindrical sheathing leaf and first above the cotyledon) has been used widely in studies on plant growth hormones. The single cotyledon remains enclosed in the old seed coat. B, seedling of typical dicotyledonous plant.

investigated also in the leaves, stems, flowers and roots of various kinds of plants at different stages in their development.

The comments that follow will touch upon such topics as the discovery of plant hormones, how their concentration may be measured, and more briefly on their chemistry, occurrence, effectiveness, formation, nomenclature, translocation, relation to normal growth, tropisms, and other life phenomena. This is essentially the outline followed by Professor Boysen Jensen in his book "Die Wuchsstofftheorie."

THE DISCOVERY OF HORMONES IN PLANTS

The history of hormone investigations extends over the past twenty-five years, and Boysen Jensen should doubtless receive credit for the discoveries which later led to the unquestioned demonstration of the presence of growth hormones in plants. His studies, published in 1910–11, indicated the presence of some sort of a chemical substance which streamed from the tip of the *Avena* coleoptile downward toward its base. If the light came from one side (hereafter referred to as *unilateral* light), the substance apparently streamed downward on the darkened side, and the coleoptile elongated on the dark side. The result was that the tip bent toward light. This was demonstrated by inserting a mica plate in a transverse direction into the back and front sides of coleoptiles, just below their tip (Fig. 2, A and B). When inserted into the back side this usual phototropic response to unilateral light did not occur. He then removed the tip of the coleoptile and placed a thin sheet of gelatin on top of the coleoptile stump. Following this, the tip was replaced in its original position—except that a layer of gelatin lay between it and the stump. When the coleoptile was exposed again to unilateral light, the usual phototropic bending took place. This led to the important conclusion that the movement of a chemical substance must be involved in this growth response.

A series of experiments by other workers followed. Paal (1918), removed the tip of the coleoptile and set it back on one side of its stump (Fig. 2 C). The result was a curvature away from the replaced tip (positive curvature), which indicated that a growth substance of some sort was moving downward from the replaced tip. Stark (1921) extracted juice from coleoptiles and made it up in agar blocks. When such an agar block was placed on one side of the coleoptile stump (see Seubert, Figure 2 D), curvature took place toward the block; this *positive* curvature indicated the presence of some sort of a growth inhibiting substance. Seubert (1925) was the first to demonstrate that growth hormone could be extracted from plant and animal material; agar blocks were prepared with saliva, diastase and malt extract, and when these were applied to coleoptile stumps (Stark's method), positive growth curvatures occurred (Fig. 2 D).

This line of investigation was followed up by Went (1928). He showed that the decapitated coleoptile tips such as Paal had

replaced on one side of the stump, could be placed on a small agar surface, and that growth hormone would diffuse out of the

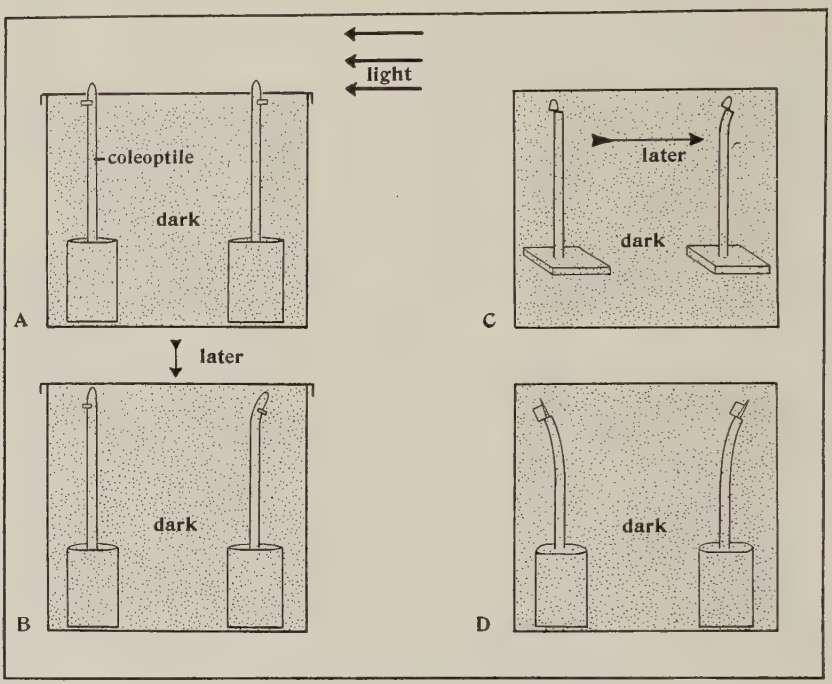

Fig. 2. A and B, diagrammatic representation of the experiments of Boysen Jensen (1910–11). A, *Avena* seedlings growing in soil in small glass containers, in total darkness except for the coleoptile tips which extend into the light (light coming from the right hand side, *unilateral* light). Before receiving the unilateral light, small sheets of mica were inserted on the front and back sides, immediately below the tips of the coleoptiles. After a short exposure to light, the coleoptiles were in total darkness. B, later, the coleoptiles with the mica insert on the side which was illuminated bent in the direction of the illumination while those with the mica insert on the back side did not bend. This indicated that a growth stimulus of some sort ordinarily passed down the coleoptile on the side away from the light, causing it to bend toward the light. (*When the coleoptile tip was severed from the stump, then replaced in its normal position but with a layer of gelatin between it and the stump, the response to unilateral light took place as usual*—not illustrated.) Boysen Jensen interpreted these experiments as indicating that the stimulus was chemical in nature, thus laying the ground work of the hormone theory. C, Paal (1918) worked with empty coleoptiles of *Coix*. After severing from the seedlings, the coleoptiles were supported in moist sand. He showed that the coleoptile tip could be removed and replaced on one side with a resulting curvature away from the tip. This indicated that growth stimulating substance was being dispersed from the coleoptile tip. D, by decapitating coleoptiles and using agar blocks according to the method of Stark (1921), Seubert (1925) was the first to show that growth hormone could be extracted from plant and animal material. When the agar was infiltrated with saliva, diastase, or malt extract, and small blocks of such agar were placed unilaterally on *Avena* coleoptile stumps, growth curvatures occurred (right). Curvatures toward the block were induced (left) when growth inhibiting substances were present in the agar.

tips into the agar (see diffusion from leaf in Fig. 3). He cut the agar into small blocks, and if such blocks were placed unilaterally on coleoptile stumps, positive curvatures were obtained, like those of Seubert a few years before. Then Went discovered that this curvature was proportional, within limits (angles of 15° to 20°) to the amount (later shown to be concentration) of growth hormone present in the agar. This marked the discovery of a *quantitative* method for working with plant hormones; the method (Fig. 3) makes it possible to determine hormone *concentration*, and its importance cannot be overestimated. The field has been an increasingly active one ever since Went's discovery.

METHOD FOR DETERMINING THE CONCENTRATION OF AUXIN IN AN UNKNOWN

No chemical test has been devised which provides a ready and simple means of qualitative or quantitative detection of the minute amounts of auxin present in living plants. This means that some other means must be used for detection. Just as the animal physiologists resort to rabbits, guinea pigs and rats for tests with animal hormones, the botanist also resorts to a biological measuring stick. The botanical "guinea pig" or test object for plant hormones, is the *Avena* coleoptile, and Went's technique, as modified by others and himself, is illustrated in Figure 3.

The laboratory in which the tests are carried on should be maintained at 79° F. and approximately 90% humidity, and pure fresh air should be supplied at regular intervals. It should be lighted only with red or orange light, of wavelengths which bring about no phototropic response in the test plants.

If for any reason it is not possible to apply the agar blocks approximately 40 minutes after decapitation, the coleoptiles may be decapitated a second time by removing a short segment at the top of the stump. After such "double" decapitation, maximum sensitivity is reached after about 3 hours.

A little more than 2 hours before a test is made, it is necessary to prepare the material in which the hormone concentration is to be determined. Let us assume that it is a vigorously growing leaf, or stem tip of the tobacco plant that is to be tested. Not knowing just what to expect at first, it would be well to use the tips of 2 or 3 plants. These are cut from the plants and placed on rectangular pieces of agar, prepared as indicated in Figure 3

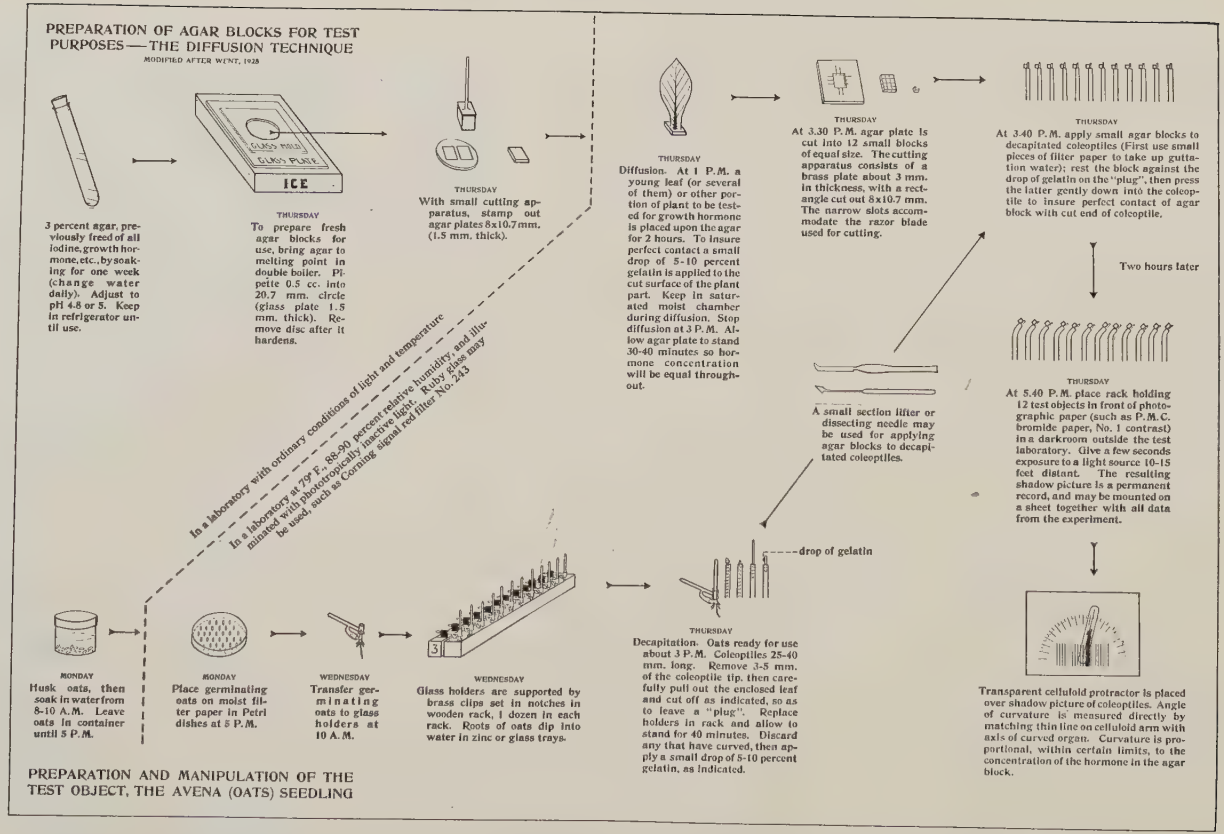
PREPARATION OF AGAR BLOCKS FOR TEST PURPOSES — THE DIFFUSION TECHNIQUE
MODIFIED AFTER WENT, 1928
ICE
3 percent agar, previously freed of all iodine, growth hormone, etc., by soaking for one week (change water daily). Adjust to pH 4.8 or 5. Keep in refrigerator until use.
THURSDAY
To prepare fresh agar blocks for use, bring agar to melting point in double boiler. Pipette 0.5 cc. into 20.7 mm. circle (glass plate 1.5 mm. thick). Remove disc after it hardens.
THURSDAY
With small cutting apparatus, stamp out agar plates 8x10.7 mm. (1.5 mm. thick).
THURSDAY
Diffusion. At 1 P.M. a young leaf (or several of them) or other portion of plant to be tested for growth hormone is placed upon the agar for 2 hours. To insure perfect contact a small drop of 5-10 percent gelatin is applied to the cut surface of the plant part. Keep in saturated moist chamber during diffusion. Stop diffusion at 3 P.M. Allow agar plate to stand 30-40 minutes so hormone concentration will be equal throughout.
THURSDAY
At 3.30 P.M. agar plate is cut into 12 small blocks of equal size. The cutting apparatus consists of a brass plate about 3 mm. in thickness, with a rectangle cut out 8x10.7 mm. The narrow slots accommodate the razor blade used for cutting.
THURSDAY
At 3.40 P.M. apply small agar blocks to decapitated coleoptiles (First use small pieces of filter paper to take up guttation water); rest the block against the drop of gelatin on the "plug", then press the latter gently down into the coleoptile to insure perfect contact of agar block with cut end of coleoptile.
Two hours later
THURSDAY
At 5.40 P.M. place rack holding 12 test objects in front of photographic paper (such as P.M.C. bromide paper, No. 1 contrast) in a darkroom outside the test laboratory. Give a few seconds exposure to a light source 10-15 feet distant. The resulting shadow picture is a permanent record, and may be mounted on a sheet together with all data from the experiment.
In a laboratory with ordinary conditions of light and temperature
In a laboratory at 79° F., 88-90 percent relative humidity, and illuminated with phototropically inactive light. Ruby glass may be used, such as Corning signal red filter No. 243
A small section lifter or dissecting needle may be used for applying agar blocks to decapitated coleoptiles.
drop of gelatin
THURSDAY
Decapitation. Oats ready for use about 3 P.M. Coleoptiles 25-40 mm. long. Remove 3-5 mm. of the coleoptile tip, then carefully pull out the enclosed leaf and cut off as indicated, so as to leave a "plug". Replace holders in rack and allow to stand for 40 minutes. Discard any that have curved, then apply a small drop of 5-10 percent gelatin, as indicated.
Transparent celluloid protractor is placed over shadow picture of coleoptiles. Angle of curvature is measured directly by matching thin line on celluloid arm with axis of curved organ. Curvature is proportional, within certain limits, to the concentration of the hormone in the agar block.
MONDAY
Husk oats, then soak in water from 8-10 A.M. Leave oats in container until 5 P.M.
MONDAY
Place germinating oats on moist filter paper in Petri dishes at 5 P.M.
WEDNESDAY
Transfer germinating oats to glass holders at 10 A.M.
WEDNESDAY
Glass holders are supported by brass clips set in notches in wooden rack, 1 dozen in each rack. Roots of oats dip into water in zinc or glass trays.
PREPARATION AND MANIPULATION OF THE TEST OBJECT, THE AVENA (OATS) SEEDLING

Fig. 3. Went's (1928) quantitative method of demonstrating the hormone content of plant parts. The time schedule is indicated by days for convenience sake only. The curvature of the *Avena* coleoptile is proportional, within certain limits, to the concentration of the growth hormone.

In our laboratory we use the size agar plate suggested by Dolk and Thimann: 8 x 10.7 x 1.5 mm. It dries out less rapidly than the smaller blocks. A small amount of 5 or 10% gelatin is applied to the cut end of the young tobacco stems and they are placed upright on the agar, then allowed to stand in a moist chamber for 2 hours. After removing the tobacco tips at the end of the 2 hour period, the agar is cut into 12 small pieces of equal size. In the meantime the coleoptiles have been decapitated, and we are ready to proceed. Each of the blocks is placed as indicated (Fig. 3) on a decapitated coleoptile. After the agar blocks have been in place 2 hours, the rack of 12 test plants may be photographed (shadow picture on bromide paper is simplest). The angles of curvature can then be determined with a protractor, and the results may be expressed in degrees of coleoptile curvature, or in the various units suggested by different authors. Curvatures up to about 20° are directly proportional to the concentration of the hormone present in the agar block.

If a liquid of unknown hormone content is to be tested, the agar should be made up with various dilutions of the unknown. Each of these dilutions should be tested, so that certain of them, at least, will fall within the range of quantitative results.

A typical schedule for diffusion of plant material and the subsequent tests is as follows:

Material	Start Diffusion	Stop Diffusion	Decapitate	Apply Agar Blocks	Photograph
A	9:00 a. m.	11:00 a. m.	10:50	11:32	1:32 p. m.
B	9:15	11:15	11:05	11:47	1:47
C	9:30	11:30	11:20	12:02	2:02
D	9:45	11:45	11:35	12:17	2:17
E	10:00	12:00	11:50	12:32	2:32
F	10:15	12:15	12:05	12:47	2:47
G	10:30	12:30	12:20	1:02	3:02
H	10:45	12:45	12:35	1:17	3:17
I	11:00	1:00	12:50	1:32	3:32
J	11:15	1:15	1:05	1:47	3:47
K	11:30	1:30	1:20	2:02	4:02
L	11:45	1:45	1:35	2:17	4:17
M	12:00	2:00	1:50	2:32	4:32
N	12:15	2:15	2:05	2:47	4:47
O	12:30	2:30	2:20	3:02	5:02
P	12:45	2:45	2:35	3:17	5:17

For one operator to run 16 dozen test plants in a little more than 8 hours, as outlined above, requires experience. It is

possible to run half as many with greater ease. With half the number, diffusion can be started at 5 minute intervals, then the operations will not overlap. With a little practice it is possible to decapitate a rack of one dozen coleoptiles in 2 or 3 minutes. Agar blocks can be applied in a similar length of time. In order not to get behind schedule if anything unforeseen happens, it is well to allow at least 5 minute periods between diffusions.

There are other ways than the *Avena* method of detecting the presence of the auxin, but they have not been as satisfactory in terms of quantitative results. Of course the *Avena* technique does not work for all kinds of plant material, but in most instances it has proved itself useful. Skoog (in press) has shown that by removing the cotyledon and endosperm from the *Avena* seedling ("de-seeding"), its sensitivity as a test object can be increased. *Cephalaria* is a sensitive test object, but it does not give curvatures proportional to concentration over a very wide range.

CHEMISTRY AND OCCURRENCE

To date three hormones have been demonstrated as occurring naturally in plants. In certain fungi it has been possible to demonstrate the presence of a growth hormone which Kögl, Haagen Smit & Erxleben have referred to as *heteroauxin*. From various higher plants and other sources these same investigators have isolated two other hormones, designated by them as auxin *a* and auxin *b*. The information they have given us constitutes the greater part of our present knowledge of the chemistry of auxins. The empirical formula of heteroauxin is $C_{10}H_9O_2N$; of auxin *a*, $C_{18}H_{34}O_5$; and of auxin *b*, $C_{18}H_{30}O_4$. Auxin *a* is a monocyclic tri-hydroxy-keto carboxylic acid with one double bond, and heteroauxin is 3-indole acetic acid, a compound known for 50 years before its potency as a plant hormone was discovered.

Pure crystals of auxin *a* are reported to have a melting point of 196° C; auxin *b* of 183°C and heteroauxin of 165°C. Auxin *a* is stable in the presence of acid and is sensitive to alkali. Heteroauxin is just the opposite, while auxin *b* is destroyed by both acids and alkalies. Auxins *a* and *b* lose their activity after a few months. They have not yet been synthesized.

Although the above compounds have diverse chemical characteristics, they apparently all promote cell elongation (in their naturally occurring state) in the direction of the long axis of stems or other parts of the shoots of plants.

The chief experimental source of auxins has been from human urine, about 80% of the growth hormone concentration of which is auxin *a* and 20% heteroauxin. The content in urine is appreciable following the ingestion of butter, salad oil and other fats at meals. Normal and pathological animal tissues have been shown to have auxin present in them. Auxins have been shown to occur also in numerous plant products, such as corn oil and malt, and in the vegetative and reproductive parts of many kinds of mono- and dicotyledonous plants. Pollens of many kinds of plants are an especially rich source, as are the embryo and endosperm of many seeds. Fungi such as *Rhizopus* and *Aspergillus* produce heteroauxin, and the alga *Valonia* has been found to contain auxin. There is every reason to suppose that these or similar growth hormones occur universally in plants.

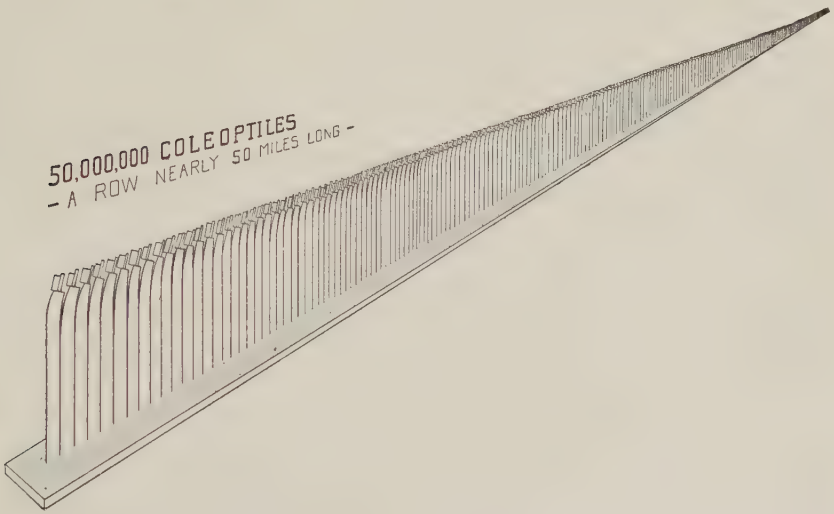

Fig. 4. One milligram of pure auxin *a* is sufficient to bend 50,000,000 coleoptiles to an angle of 10°, if applied unilaterally in agar blocks. 50,000,000 coleoptiles, if placed side by side, would make a row nearly 50 miles long. At this rate, four pounds of auxin *a* would bring about a 10° curvature in a row of coleoptiles extending from earth to sun!

EFFECTIVENESS

Auxins *a* and *b* are about equally effective in promoting growth. It has been estimated that one milligram of either compound is capable of bringing about a curvature of 10° in fifty million decapitated coleoptiles, if applied unilaterally in agar blocks, as previously indicated. Convert this into some figure that is more nearly comprehensible. There are a few over

one million coleoptiles to the mile if they stand closely side by side, so one milligram of either compound is capable of bringing about a 10° curvature in nearly 50 miles of coleoptiles (Fig. 4). Heteroauxin is approximately one-half as effective, i. e., one milligram of it would bend only 25 miles of coleoptiles!

Substances of synthetic origin (other than 3-indole acetic acid) have been tested on the *Avena* coleoptile, but none tested so far has been quite as effective as the naturally occurring auxins. For example, one milligram of one of the indole propionic acids would bend 5 miles of coleoptiles, and the same amount of a methyl-indole acetic acid would bend only 1½ miles of coleoptiles, etc. These synthetic substances have been designated as "growth substances," and indeed many of them do appear to behave as such. It may be that the concentrations in which it is necessary to use them to get a given effect will be so high that they cannot be considered hormones. They do not need to concern us for the present for they have not been shown to occur naturally in plants. But that they are of the utmost practical importance, whether hormone-like or not, cannot be denied, and their applications in horticulture with regard to rooting and other phenomena will be discussed by Dr. Zimmerman in a later lecture in this series.

NOMENCLATURE

Any chemist would tell us that even with our present knowledge of the chemistry of plant growth hormones, we ought to call them by their chemical names. For example auxin *a* is auxentriolic acid, auxin *b* is auxenolonic acid, and heteroauxin has already been referred to as 3-indole acetic acid. But there are many brands of chemical nomenclature. 3-indole acetic acid is also known as β-indolyl acetic, β-indole acetic and indole-3-acetic acid. We might well adopt the names botanists have provided, such as growth substance[1], growth regulator[2], growth hormone and phytohormone; they refer more particularly to the physiological response. The animal hormonists have outdone the botanists, and a score or more of physiological names have been applied to sex hormones alone. The nomenclature will become more settled as our knowledge of the field advances.

[1–2]The terms "growth substance" and "growth regulator" probably ought to be dropped gradually from the literature, because the nutritional substances even when present in very small amounts (minerals, gases, and organic foodstuffs) are also growth substances and growth regulators.

FORMATION, STORAGE, AND PHYSIOLOGICAL REGENERATION

We are almost entirely in ignorance regarding the synthesis of auxin by the living plant. The production of heteroauxin by molds and bacteria has been studied in relation to the character of the nutrient substratum; it has been found that glucose, peptone, glucose ammonium tartrate, tryptophane and other compounds favor its formation. Within limits, higher temperatures have been found to result in increased production of growth hormone. It has been found too, that its formation in young leaves and other growing parts of green plants will not take place in the absence of light. Seedlings are enabled to grow for many days in darkness because they have a stored supply of auxin present in the seed; when this is exhausted they cannot grow further, even though they possess adequate food and water. Just how this auxin is stored in seeds we do not know. Presumably it is in an inactive form, and does not become active until the seed absorbs water. Some seeds require a short exposure to light before they will germinate. This doubtless indicates that light in some instances activates in some way the inactive stored form of auxin.

There are many references in the literature which indicate that growth hormone is formed at the tip of the *Avena* coleoptile, from which point it moves downward, bringing about growth. From what we know now, this interpretation seems untenable. It is more likely that the auxin, probably in its inactive form, is moved from the endosperm and cotyledon upward through the vascular bundles to the tip of the coleoptile, where it becomes activated before being dispersed downward.

There are many studies pertaining to "physiological regeneration," a phenomenon peculiar to the coleoptile of grasses, and which may be explained as follows: When the coleoptile tip is removed, the immediate source of the growth hormone supply is removed also and the growth of such a decapitated coleoptile, as would be expected, gradually comes to a stop, i. e., the hormone present in the tissues of the coleoptile stump is used up. At this time the coleoptile is not responsive to unilateral light or to gravity. But after a few hours a new "physiological tip" becomes established at the upper end of the stump; as the auxin moves downward through the tissues from this new center of dispersal, growth starts again, and the organ again is sensitive to unilateral light and to gravity. This physiological regenera-

tion, as it is called, is probably not "regeneration" in the sense originally intended. As we now understand it, the endosperm and embryo are places of storage of growth hormone, and its probable movement upward in the vascular bundles has been indicated above. If the endosperm is removed, physiological regeneration does not occur after about ten hours have elapsed. From this it might reasonably be expected that it would move upward (in its inactive form) in a decapitated coleoptile as well as in an intact one, and that it would similarly be dispersed downward (in its active form) after the wound shock has subsided. There is considerable evidence to support this interpretation but the secret of "activation" at the tip, if this is what happens, still remains to be discovered.

MOVEMENT OF THE GROWTH HORMONE IN PLANTS

This is a subject of utmost interest. The naturally occurring growth hormones apparently move only in a morphologically basipetal direction, as for example, from the tip downward in the *Avena* coleoptile, or from the embryological regions of young stem tips downward in stems, or downward from the storage place in the cotyledons into the hypocotyls of dicotyledonous seedlings. This one-way movement has been designated as "polar" transport. It apparently holds true in young or moderately mature tissues, but in old tissues the growth hormone has been demonstrated to move in either direction. Of course it does not ordinarily occur in mature tissues. Anesthetization disturbs the "polarity" of transport.

It has been discovered recently that certain of the synthetic growth hormones can be applied to the plant and be transported upward. This apparently is due to their getting into the transpiration stream, in which they are carried upward through dead xylem ducts. This is not out of harmony with the facts given above in regard to polar movement through living tissues.

The velocity of movement is about 1 centimeter per hour, a rate considerably greater than could be accounted for by diffusion; the *rate* apparently is not affected by ordinary ranges of temperature and is independent of any concentration gradient existing in the plant. Anesthetization reduces this rate to that of simple diffusion.

Several explanations have been offered to explain the mechanism of movement: diffusion, protoplasmic streaming, electrophoresis, etc. The latter has found considerable support

in studies of the past year or two. The acid character of the growth hormones suggests that they might be moved toward the positively charged pole in an electrical circuit, an explanation which has been reported as verified experimentally *in vivo* and *in vitro*, under an applied electric potential. This does not mean that protoplasmic streaming and other factors are not involved. Our information on this, as on other things, is as yet incomplete.

GROWTH HORMONES AND NORMAL GROWTH

From what has been said it is clear that we are dealing with minute amounts of certain chemical substances which are synthesized by plants. These substances move and "behave" characteristically, and most important of all, *growth* depends upon their presence. Cells apparently cannot elongate without them.

If auxin applied in agar blocks to decapitated *Avena* coleoptiles gives curvatures proportional to concentration, there ought to follow a direct correlation between growth intensity and hormone concentration in normally growing plant organs (within limits, of course). This has been demonstrated in a few plants—in the *Avena* coleoptile, lupine hypocotyl, and the foliage leaf of tobacco. The implication is an important one: growth vigor, other things being equal, must be associated with the synthesis, accumulation, effective use, or destruction of auxin. Van Overbeek (1935) reports that a dwarf strain of maize derives its dwarf character from the fact that enzyme systems are present which destroy the hormone more rapidly than in normal plants.

The facts regarding the normal growth of *roots* seem, at first glance, to be in opposition to the thesis of the growth substance theory. Root growth is inhibited by concentrations of the hormone which ordinarily promote growth in stems, coleoptiles, petioles of leaves, etc. While this may give us a clue to the inherent difference in roots and shoots, it is without an entirely satisfactory explanation in terms of growth hormone. But certain investigators regard it as the normal and expected behavior. The argument is this: When a root is decapitated, the growth of its stump is accelerated for a short time, and if the root tip is placed unilaterally on the stump, growth is *inhibited* on that side (curvature *toward* the root tip); the response is the same if a coleoptile tip is placed unilaterally on the root stump, although

we know that a root tip or coleoptile tip placed unilaterally upon a decapitated coleoptile gives a growth promoting effect (curvature *away* from the applied object). If a root is immersed in an auxin solution, its growth in length may cease entirely. This can mean but one thing: the normal response of roots to auxin applied in the manner indicated is to slow down their growth rate, i. e., growth inhibition. As regards roots, then, the auxins are not growth promoting hormones; they are growth inhibiting! Concentration of hormone may turn out to be the answer to this puzzling difference between roots and shoots.

A discussion of normal growth ought to include some mention of how hormones actually work, i. e., their mechanism of action. There is evidence that they are used up in the process, not as building stones, but as activators influencing in some way the plasticity of cell walls. The walls become stretched in growth and do not shrink back to their previous smaller size. There must be either a rearrangement of the structural units of the cell wall, or an active deposition of new wall building material. The first urge for a cell to grow may come from wall extension, the wall taking the lead and thus making possible the entrance of more water. Although in its movement the auxin passes through the end walls of cells, only the side walls are affected—they are the ones which increase their length. There is a real challenge here. We do not know the fundamentals.

TROPISMS

It was brought out in the brief history of the subject that Boysen Jensen's discovery came about through experiments on the response of the coleoptile to unilateral light. This phenomenon of phototropic response is well known, and we expect it whenever a potted plant is placed near a window in our house. Its younger stems always bend toward the light. Any such response must be due to unequal growth on the opposite sides of a light-stimulated organ. The darkened side grows more rapidly than the lighted side. It has been shown that when a young stem is given light from one side only, the growth hormone becomes unequally distributed. More of it is transported to the darkened side, hence a greater concentration of it on the darkened side. Greater concentration of the hormone on the darkened side of the stem gives what might be expected, i. e., greater growth on that side. The result: bending toward the light. Exactly how light brings about this differential distribu-

tion of the hormone, we do not know, but from the suggestions already made in connection with movement of auxin in the plant, we would be led to suspect that it is at least partly due to a light-induced change in the electric potential across the organ.

The usual responses of stems of plants to gravity are well known also; if a potted plant is oriented on its side we know that in a short time the young main stem and leaves will turn upward—the so-called "negatively geotropic" response. The work of Dolk and others has shown that this is due to the greater accumulation of the hormone on the under side of an organ such as a coleoptile or stem, hence *more rapid cell elongation on the under side*, and the resulting upward curvature.

Roots behave differently. That the main roots of most plants grow directly toward gravity is common knowledge. If they are placed in a horizontal position, the young growing tip turns downward, i. e., *the cells on the upper side* elongate more rapidly, and cause the growing tip to bend downward. It has been shown that this is due to the accumulation of the hormone on the lower side of the root, where its presence inhibits cell elongation; hence the root tip turns downward in its growth.

Here, then, is the connecting link between the environment and the growing plant. The tropic responses of plants to two of the most important stimuli in their environment, light and gravity, are brought about by the same agent, the growth hormone which occurs naturally in their tissues. This has come to be known as the growth hormone explanation of tropisms. Although some of the details of our explanation may be incorrect, the evidence is overwhelming, and strikingly simple.

Tropic responses can be induced in young portions of plants by applying growth hormone to the outside of the plant in some suitable solvent such as lanolin, but this is to be discussed by others.

THE RELATION OF HORMONES TO OTHER LIFE PROCESSES

Most of what has been said up to this point finds its explanation in the fact that plant growth hormones regulate cell elongation. Other work reported in the past year or two suggests that numerous other effects may be due in whole or in part to the activity of these same hormones: (1) It has been reported that they stimulate the production of new roots. (2) The so-called apical dominance of the terminal bud over the lateral buds has been attributed to the inhibition of the lower axillary buds by

growth hormone moving downward from the terminal bud past them. (3) Cell division in the cambium and in callus tissue has been attributed to auxin also. These observations are of great interest and are very suggestive. Whether the effects mentioned will utimately be attributed to hormones remains for future investigations to determine.

SUMMARY AND CONCLUSIONS

Plant hormones (auxins), like animal hormones, are produced in very small quantities in one part of the organism (young, vigorously growing parts) and moved to another part where they become active. Their main role, as we now understand it, is the regulation of cell elongation; other roles have been attributed to them.

The tropic response of plants to two of the most important stimuli in their environment, light and gravity, are brought about by the movement of auxin from one part of a stimulated plant organ to another. This has come to be known as the growth hormone explanation of tropisms.

Three different hormones have been found to occur naturally in plants: auxin *a* and auxin *b* in higher plants, and heteroauxin in the fungi. Although chemically distinct, they are not yet known to differ in their effect on growth.

A few years hence the picture presented here will change materially. We have just started to work with a new tool that should aid in probing further the secrets of plant development. Every great surge of progress in our understanding of growth has come about from the discovery and use of just such a new tool. This augurs well for the future of our knowledge of chemical correlation in plants, and, indeed, for our understanding of plant morphogenesis as a whole.

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RESPONSES OF PLANTS TO HORMONE-LIKE SUBSTANCES

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My assignment concerns the work at the Boyce Thompson Institute with plant hormones and chemical compounds which induce a hormone-like response. The program committee was kind enough to have my paper preceded by one from Dr. Avery dealing with the historical phases of the subject. I will limit myself, therefore, to the work at the Institute. What I have to say involves also the work of two of my associates, Drs. A. E. Hitchcock and Frank Wilcoxon, plant physiologist and chemist, respectively. I wish to fully recognize the part they have taken in the work, though I shall not attempt to point out individual contributions. Dr. William Crocker, Director of the Institute, has also maintained a very active interest in our work on growth-promoting chemicals, especially as related to unsaturated carbon gases.

In recent years several terms have been used to designate growth-promoting substances (plant hormones, growth hormones, growth substances, growth regulators, auxins, etc.). As used in this paper, the following definitions will apply: *Plant hormones* are substances, produced by the plant and which exert a regulatory influence on growth and development of the organism. As far as green tissues are concerned, these "substances" have been shown to exist but not one has been chemically identified. Hormones are present in minute amounts and must not be confused with materials having a direct nutritive effect. *Natural growth substances* carries the same meaning as "hormone." *Auxin*, or hetero-auxin, is used to designate "Auxin A" or "B" or indoleacetic acid, which were extracted from urine, corn meal, etc. (but not green tissue) and assigned chemical formulae by Kögl. They are therefore classed with other known chemical compounds which induce hormone-like responses in plants. *Synthetic growth substances* are any chemical compounds which, when applied locally or otherwise, induce hormone-like responses in plants. They include compounds that cause bending, swelling, proliferations, and overgrowths of

stems and leaves, and in some cases the induction of adventitious roots. As to form, they may be acids, salts, esters, or gases.

During the past few years, 32 growth-promoting substances have been reported. Among them are 14 acids, 11 esters, and four unsaturated carbon containing gases. Also salts of the various acids are effective.

The most important substances from a scientific standpoint are naphthaleneacetic acid, indoleacetic acid, indolebutyric acid, indolepropionic acid, fluoreneacetic acid, phenylacetic acid, ethylene, propylene, acetylene, and carbon monoxide. For practical plant propagation, naphthaleneacetic acid and indolebutyric acid are the most important.

The tomato plant has been extensively used as a test object when effective chemicals were being compared or when new compounds were tested for activity. Many other species, however, serve the purpose as well as tomato. Details of the tests will be mentioned later.

A simple method for applying substances locally is to mix a given amount of the chemical with a known quantity of lanolin (wool fat) and apply the preparation with a glass rod to the part of the plant to be treated. A one per cent mixture is usually convenient at the start. If this is found too strong (as would be the case with naphthaleneacetic acid) it can be readily diluted with pure lanolin. Other carriers, as paraffin oil, olive oil, etc., might be found more useful than lanolin for some purposes.

Water solutions of growth substances are effective over a wide range of concentrations from 1 part in 5,000 to 1 part in 1,000,000. The dilutions must be varied according to the substances and the uses to which they are put.

In 1933 three papers (9, 10, 11) reported that four unsaturated gases (carbon monoxide, ethylene, acetylene, and propylene) induced epinasty (due to accelerated growth on the upper side of the petiole) and initiated adventitious roots on stems and leaves of many species of plants. These responses involved cell enlargement, cell division, and the organization of cells for the production of adventitious organs. The gases were applied to the entire plant or to a single root or leaf with the result that the chemical moved into the tissue and spread throughout the plant, causing a systemic response (Fig. 1A). The gases were also dissolved in water and applied in solution with similar effects.

Figure 1. Tomato plants. A., Left, control; middle, treated with one part of ethylene gas to 500,000 parts of air. Photographed 24 hours later. Right, treated on the upper side of the petioles with a lanolin preparation containing 0.1 per cent naphthaleneacetic acid. B., Left, control; right, cut surface treated with 1.0 per cent naphthaleneacetic acid. Photograph taken eight days later.

Beginning in 1934 the responses induced by the simple compounds (gases) were compared with responses induced by more complex substances, ring compounds (2). Though administered in a different way, the end results were about the same for both groups of chemicals. The crystalline compounds have the advantage of being easily applied in water, oil, or lanolin, inducing either local or systemic responses.

The following are some of the responses to be considered: Local acceleration of growth causing bending of stems and leaves (epinasty); systemic responses vs. local; swelling and proliferation of treated tissue; cell division and induction of adventitious roots; acceleration of growth following retardation; and retardation of root elongation followed by increase in diameter and induction of adventitious roots.

When lanolin preparations of growth substances are applied to the upper side of a tomato petiole, growth is accelerated locally and the result is downward movement of the leaf (Fig. 1A). The degree of movement varies with the concentration of the substance and the age or condition of the leaf.

Similarly, if a growing stem is treated on one side with a low concentration, the growth rate is increased and the stem is caused to bend away from the treated side (negative bending). If the concentration is too high, growth is retarded and the stem bends toward the treated side (positive bending).

Local application of very low concentrations induces only a local response, but if high concentrations are used the substances are translocated and tend to induce a systemic response as shown by epinasty of leaves beyond the treated region. As with gas-treated plants, the upper side of the petioles respond first and, therefore, the downward growth of the leaf. The systemic effect is readily induced by injecting a water solution into the tissue or by watering the soil with a solution of the substance. To inject the substances it is well to use a glass tube holding 0.3 cc. and drawn to a capillary at one end. Insert the capillary into the stem and allow the contents to drain into the tissue. The time required varies with the plant, the weather conditions, and the time of day. Usually two to four hours are sufficient if the plant is in a light, dry, place. For this purpose use approximately 0.1 mg. of the substance per cc. of water. When the solution is added to the soil, use 10 to 40 mg. in 50 cc. of water, depending upon the activity of the substance and the size of the plant. An 8-inch high tomato plant in a 4-inch pot will

respond when 20 mg. of indolebutyric acid in 50 cc. of water are used. Half of that concentration is sufficient for naphthaleneacetic acid or indoleacetic acid.

Bending responses can be detected within one to two hours after the substance is applied. The activity continues and the response is complete within six to ten hours. Within 48 hours another kind of activity, swelling of the tissue, becomes evident. This phase of the response is associated with cell division and the activity may continue until the stem breaks open or ruptures the epidermis. Proliferations and gall-like growth occur when some kinds of plants are used. These are sometimes compared with crown galls or tumors. They differ, however, in that they do not continue to grow long after the substance is removed. Crown galls continue to grow as long as living organisms are present, but malignant tumors of animals are not so regulated. The tumor seems to provide its own stimulus once initiated.

A third type of response becomes evident within five to ten days when adventitious roots begin to make their appearance. Stems, leaves, flower stalks, and young fruit can all be induced to form roots while the plant is intact. If the top of a growing plant is removed and the chemical applied to the cut surface, a crown of roots soon appears (Fig. 1B).

There is considerable variation in the root-inducing power of the growth substances applied to intact plants, naphthaleneacetic acid being the most effective and the phenyl compounds among the poorest. The latter often cause much swelling with few or no roots while indolebutyric acid may cause little swelling and many roots.

There is an important difference between the response of stem tissue and that of roots. Cells of growing stems can be increased in length by treatment with growth substances. That is the cause of bending when the chemical is applied unilaterally. Cells of root tissue on the other hand not only do not increase in length when treated, but are actually retarded by the substance. When aerial roots of Cissus are treated with comparable concentrations along one side with only a trace of growth substance, positive bending results. If the tip is treated the entire region of elongation is retarded. In other respects stems and roots respond very much alike. Following treatment there is evident swelling and increase in diameter and then within three to six days numerous branch roots appear. The same substances have

been used to induce adventitious roots on roots and roots on stems. This raises the question whether there might be a group of chemicals, not now recognized, which have the power to induce shoots or other organs of plants.

Mention was made of the absorption of growth substances from the soil. The rate at which the chemicals were taken up the stem was detected by stem bending and epinasty of the leaves. There was evident variations with weather conditions as with transpiration and it was assumed, therefore, that with this method of application the substance traveled in the transpiration stream. If the rate of transpiration was reduced by increasing relative humidity or placing plants in the dark, the rate of movement of the substance from the roots was also reduced.

However, responses induced by lanolin preparations applied to the aerial parts were not influenced by atmospheric conditions in the same way. Darkness or high relative humidity favored absorption from lanolin preparations through the epidermis and longitudinal movement in both directions. Apparently, therefore, movement of these substances occurs also outside the transpiration stream.

In this connection it should be pointed out that growth substances can be absorbed from water solutions through the tips of the leaves. If the tip of a tomato leaf attached near the center of an eight-inch plant is placed in a solution of naphthaleneacetic acid (10 to 30 mg. per 100 cc. of water) or indoleacetic acid, epinasty of the treated leaf occurs within an hour or two. This response is soon followed by bending of the stem and epinasty of other leaves, both below and above the treated leaf. The movement downward, however, is more rapid than upward. When treating leaves in this way it was found best to break the epidermal hairs or otherwise damage the tissue to facilitate entrance of the chemical.

CONDITIONS AND FACTORS AFFECTING THE RESPONSE OF PLANTS TO GROWTH SUBSTANCES

It was evident from the first that varying the environmental conditions changed the capacity of plants to respond when treated with any of the several growth substances. Plants in different stages of maturity, or similar plants at different seasons of the year varied in their capacity to respond to treatment. Sunlight and complete darkness brought out some facts which should be considered.

A large number of six-inch tomato plants in four-inch pots were placed in the dark room with a temperature of 75° to 80°, and each day for a week several of the plants were subjected to a series of tests. The tests consisted of treatment of leaves and stems with lanolin preparations of growth substances; subjecting the plants to an atmosphere containing ethylene gas; placing plants in a horizontal position to induce the negative geotropic response (bending away from the earth).

The summarized results are as follows: The plants lost their capacity to respond (epinasty of leaves) to ethylene gas in three days, and to the growth substances in six to seven days. When placed in a horizontal position the plants failed to right themselves after the fourth day (Fig. 2A). At this time, however, the horizontal plants could be induced to turn upward if treated on the lower side of the stem with lanolin preparations of the growth substances (Fig. 2B).

Geotropic responses are assumed to be due to a redistribution of natural hormones in favor of the lower side (8). If this theory is correct, plants losing their capacity to grow upward presumably have lost all their natural hormones. Plants in this condition should make good test objects to determine which chemical compounds act like hormones and might therefore properly be called "growth substances." On that basis all of the naphthalene, indole, and phenyl compounds mentioned at the beginning of this paper could qualify (3).

It appears that growth responses involve a chain of essential compounds. If any one is missing there can be no growth. The plants in dark for several days lose their natural hormone (1) which has to do with geotropic response and, therefore, cannot right themselves when placed in a horizontal position. The growth substances have been substituted for the "missing link." It could be further assumed that if any essential elements, for example sugar, were absent there could be no growth until a satisfactory substitute was supplied. Perhaps the substitute could be another sugar different from the natural product.

There was some relation between the food storage organs and the length of time plants could tolerate darkness. Large tomato and tobacco plants lasted much longer than small ones. Plants with storage organs—dahlias, artichokes and potatoes—grown in the dark from the first, kept their capacity to respond to gravity and treatment with growth substances for 60 to 80 days (Fig. 2c).

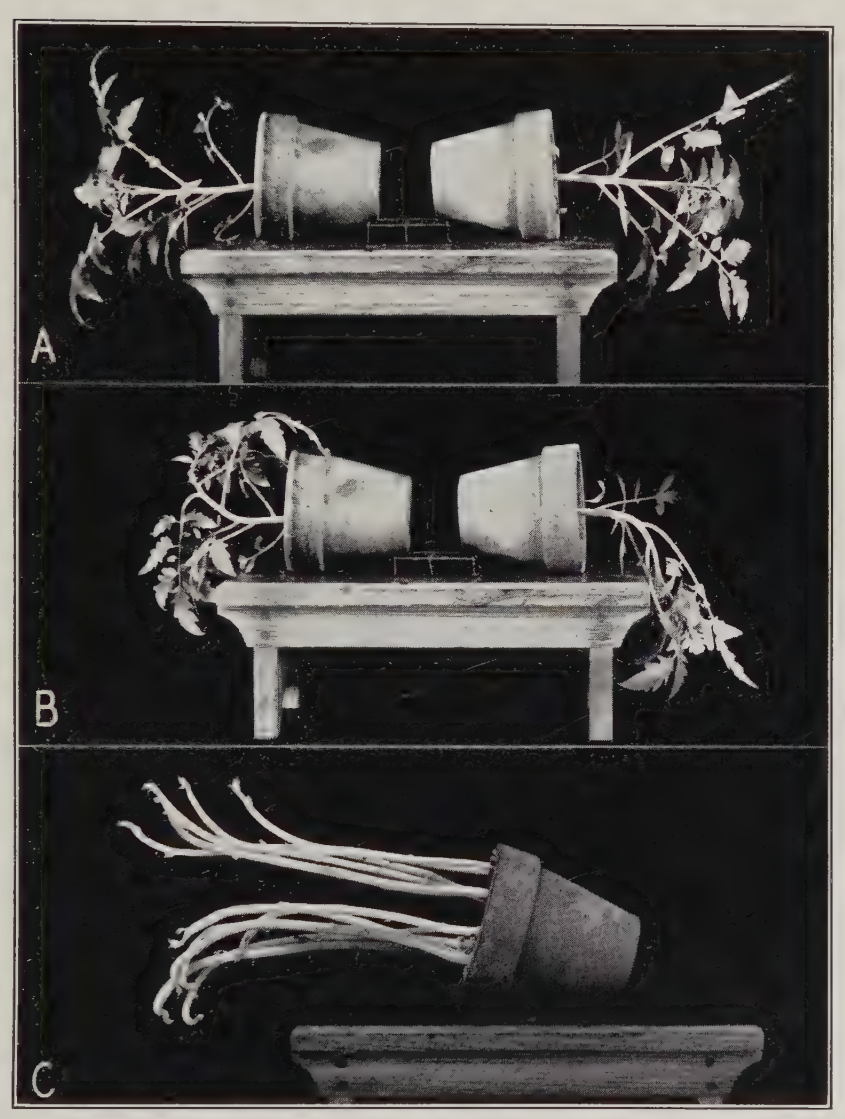

Figure 2. A., Tomato plants in the dark four days, then placed in a horizontal position and photographed 24 hours later to show loss of capacity to respond to force of gravitation. B., Same plants as in A. 24 hours after treatment with 1.0 per cent indolepropionic acid. Left, treated on under side; right, treated on upper side. C., Potato plants grown in dark for 25 days, then placed in horizontal position, at which time lower six shoots treated on upper side with naphthaleneacetic acid. Upper shoots left for controls show negative geotropism.

It appears, therefore, that light is not essential for the production of natural hormones in growing tissue if storage organs are present. On the other hand, small seedling plants (tomato and tobacco) soon lost their natural hormones if kept in continuous darkness. The rate at which small seedlings lost their hormones varied with the temperature. Plants kept at 50° F. for 10 days still responded to gravity ethylene gas and other growth substances while those at 80° lost their capacity to respond after four to six days. Transferred back to light these plants regained their capacity to respond to gravity and growth substances.

It is not clear from these data what part light plays in producing hormones in seedlings in contrast with the supply in plants having storage organs and grown in the dark.

PRACTICAL APPLICATIONS

The botanical laboratories will find many uses for growth substances.

In the search for natural hormones and synthetic compounds which induce hormone-like effects on plants, several different methods have been developed. The *Avena* method which employs the oat coleoptile as the test object is well known. This has been considered by some investigators as the standard method. To obtain reliable results with this procedure, it is necessary to use a standardized strain of oats, to maintain a constant temperature in a dark room with high humidity, and to become highly skilled in handling the equipment, conducting the experiments, and collecting the data. In fact the difficulties involved discourage all but the most persistent investigators. Another objection to the *Avena* test is that it measures only one of several growth responses induced by hormone-like substances—namely, the capacity of a substance to cause cell elongation. To satisfy all the requirements, a method should be capable of measuring cell enlargement, cell division, penetration, and the induction of new organs. At the present time no one method has been found that can fulfill all of these requirements.

The technique developed in the laboratory at the Boyce Thompson Institute makes use of the tomato plant though many other species can be satisfactorily used. No special skill is required. The chemical being investigated is mixed with lanolin or olive oil and applied to one side of the stem at the

region of elongation and on the upper side of the adjacent petiole. If the substance is active the leaf bends downward and the stem bends away from the leaf thus increasing the angle between the treated parts. This response occurs within one to six hours. After a compound is found effective, dilutions are made and compared with a known standard which is usually α-naphthaleneacetic acid. A concentration of one part of this substance to 1,000,000 parts of lanolin will induce epinasty of tomato leaves.

The same technique serves also to test the root-inducing capacity of a substance for intact plants but higher concentrations are required. The highly active substances induce roots over a range of concentrations beginning with 0.001 per cent and going up to the toxic limit which is usually around 1.0 to 3.0 per cent.

The capacity of a substance to spread throughout the plant and thus induce systemic responses is determined with the use of lanolin preparations and water solutions. The first application of lanolin preparations serves for studying induced acceleration of growth causing bending from cell enlargement, cell division, penetration, systemic response, and production of adventitious roots. Responses involving retardation and various types of proliferation can also be determined. The water solutions are added to the soil of potted plants, injected into stems and leaves, and used for tests involving immersion of leaves. Also leafy cuttings of tomato are convenient test objects for quick response. If the basal end of a six-inch cutting is placed in a solution of an effective substance, induced epinasty of leaves becomes evident within an hour or two.

Plant propagation. To test the root-inducing capacity of substances to be used in connection with propagation of plants from cuttings, *Ligustrum* and *Euonymus* are generally used. They are usually available and both hardwood and summer cuttings respond readily. The basal ends of the cuttings are placed in water solutions of the substances for 24 hours and then planted in a rooting medium. The controls under this condition start rooting in 20 days. If the substances are effective the treated cuttings will have developed roots in 14 days.

The most important substance for propagating plants by cuttings is indolebutyric acid. Naphthaleneacetic is second and indoleacetic acid third in importance. The indolebutyric is effective over a wider range of concentrations than the other substances.

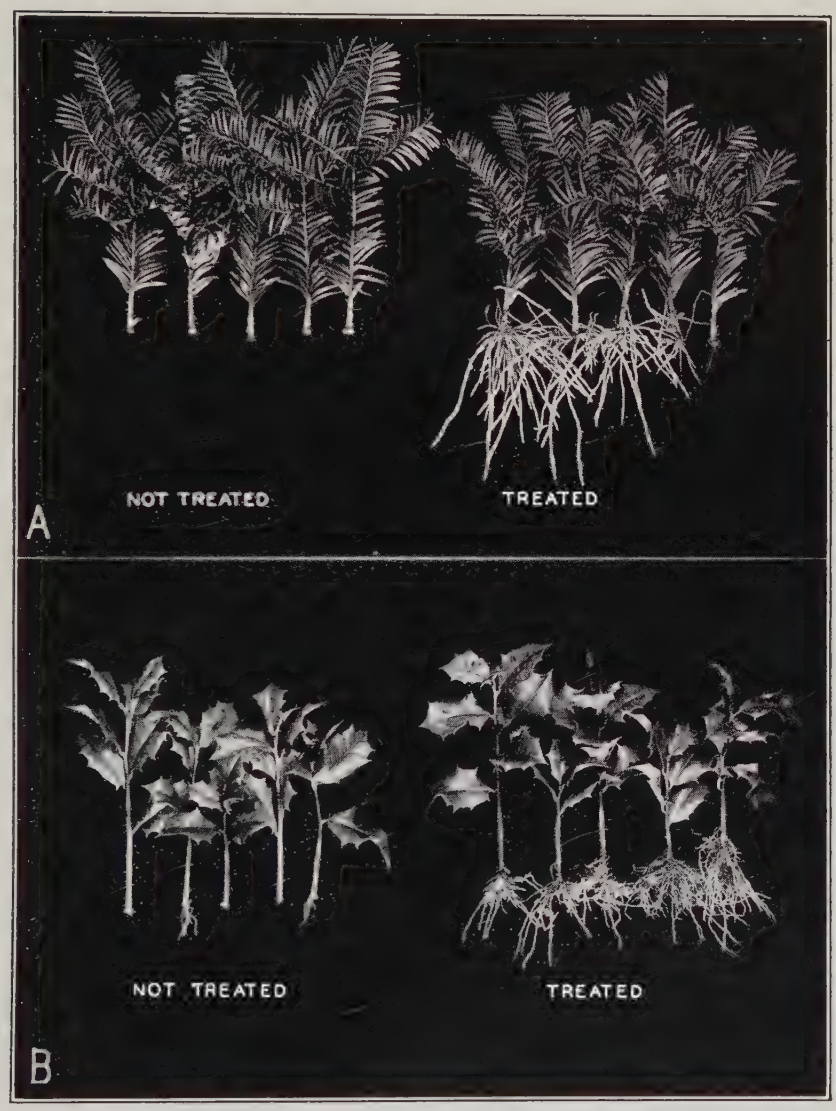

Figure 3. Cuttings treated with water solution of indolebutyric acid for 24 hours, then planted in the rooting medium. A., Taxus. B., Holly.

With the aid of this substance we have been able to hasten the rooting of species which are ordinarily propagated by cuttings and to induce roots on cuttings of species which will not root otherwise. An adequate root system can be quickly formed and the resulting plants readily established. Some of the difficulties encountered in the past with plants from cuttings concerned a meager root system. This phase of the problem can now be eliminated.

The question is often asked, do these chemically treated cuttings produce normal roots? The only answer I can make is that the resulting root system appears normal and after being planted in soil the new plant is readily established.

Approximately eighty-five genera, involving several hundred species and varieties, have been found to make satisfactory response when given the chemical treatment. Taxus and holly (Fig. 3) can be rooted in half the time required ordinarily for control cuttings. Both young and old wood work equally well. Roses and dogwood are among the most sensitive types responding in a very short time to low concentrations of the substance. Apples and pears vary with the variety. They do not respond when hardwood cuttings are used but several varieties can be propagated readily from treated greenwood cuttings. In general, leafy cuttings of all species respond better than leafless, hardwood types. The difficulty may be that the leafless cuttings do not take up the material from solution. However, it has been encouraging to find that many species respond when both hardwood and green cuttings are used.

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More Astronomy for the Millions

It is evident from the title and text that the author of this book has read the several previous attempts to make a knowledge of the universe available to the "millions." He has examined the results, found them wanting and turned his own efforts to rectifying the deficiency. His satisfaction in his work is one of the outstanding features of his book.

Judged objectively, "Astronomy for the Millions" is a poor book. It abounds in exclamation points and adjectives, such as "amazing," "incredible," "magnificent," and others of the Hollywood type. The sentence structure is frequently atrocious, lacking in subject or predicate or sometimes both. Paragraphs often begin with expletives and end in confusion. The author conveys the impression that he is striving to achieve clarity of exposition by raising his voice. He is given to the use of literary devices such as discovering the fragments of a diary written by a man who had made a trip to Mars. It does not appear that the device helps the understanding of conditions on the planet very much. It is in fact misleading because it allows the reader to believe that we know a great deal more about the Red Planet than is in fact the case.

"Astronomy for the Millions" is misleading in more than this one respect. There are several short passages that are open to question. Of the longer treatments, one of the most misleading is a discussion of the expanding universe in which the author does little to indicate that the observational evidence has not yet given full support to the theory. Hubble, an authority on the subject, even says that the data now available seem to show that the universe is **not** expanding.

The author, in short, tries too hard and stoops too much. Such a story would have been better told in forthright language of great simplicity.—C. E. HESTHAL.

Astronomy for the Millions, by G. Van Den Bergh. xi+370 pp. New York, E. P. Dutton and Company, 1937. $3.50.

NERVOUS SYSTEM AND INTERNAL SECRETION

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Internal secretion has become a problem of widespread interest since an overwhelming array of facts has been found showing that hormones are the fundamental and indispensable instruments by which the functions of the animal body are regulated and coordinated. To a great extent life as a whole is integrated by hormones. Former discoveries in this field led, and with reason, to a growing belief that, as Sterling expressed it, chemical regulation is not only the older but also the more widespread and fundamental form of coordinatory mechanism.

This latter view eventually led to a lesser estimation of the nervous system, to which, up to that time, had been ascribed the preponderant influence as regulator of functions. Too, another factor has contributed for quite a time to studying internal secretion without regard to the central nervous system, namely, that hormones appear to act whether a tissue is innervated or not. Internal secretion apparently continues even after all connections between the nervous system and glands of internal secretion have been severed.

On the other hand, the question whether hormones had any influence on the nervous system has not received sufficient attention. This neglect was for a time justified, as first of all the better defined reactions of peripheral structures and functions had to be determined, especially as the results could be expressed in more or less quantitative terms. Most valuable and trustworthy information on the activity of hormones has been obtained in this manner.

Nevertheless, earlier observations had suggested a striking influence, especially of one gland of internal secretion on the central nervous system. From the very beginning of modern study of the thyroid gland it had been recognized that young individuals with varying deficiencies of the thyroid gland developed cretinism, characterized, among other features, by inferior intelligence and mental activity. Naturally this was taken as proof that the thyroid has an influence on the central nervous system. However, the question remains open whether mental disablement is not a secondary phenomenon due to the arrested

development of the cells of the cortex of the brain. Also in young animals symptoms of mental inactivity become apparent following thyroidectomy.

To arrive at a more intimate knowledge of the relation between glands with internal secretion and the activity of the central nervous system investigation of the thyroid gland appears particularly significant, since it is especially adapted to study and has, in addition, an outstanding position as regards its influence on the central nervous system. Notwithstanding this situation we had to work out methods for quantitatively estimating this influence. It was necessary to state in exact units the intensity of the stimulus acting on the central nervous system as well as the intensity of a well-defined response. The postulated demands were fulfilled by various methods developed for our purposes in the Physiological Institute of the University of Berne.

I will begin with the reaction of the respiratory centre in the medulla. This is stimulated by CO_2. The strength of this stimulus can be quantitated by having an animal breathe air of either 20 or 40 mm. CO_2 tension. The response is then exactly measured by observing the amount of air breathed in one minute through a gasometer. When the increase of the minute volume of respiration of the normal animal inspiring these air mixtures is known, we inject the hormone of the thyroid gland, best in the form of thyroxin. The usual augmentation of respiration is increased but what is especially striking is the fact that three and a half hours after injection of thyroxin, this augmentation is already marked. It is the earliest response which thyroxin evokes, while the first metabolic effects do not appear before 24 hours. This time relation is significant as it shows that the primary effect of the internal secretion of the thyroid is on the central nervous system. After thyroidectomy the reaction is reversed and the excitability of the respiratory centre is much lower. The opposite changes in excitability after injection of thyroxin and after thyroidectomy are also noted if one records the frequency of respiration of animals subjected to raised environmental temperature; the increase, compared with the normal animal, is greater after thyroxin, and smaller after extirpation of the thyroid.

It is of interest that extirpation of the spleen acts in the same direction on the respiratory centre as an increase in the activity of thyroid gland. This suggests that as long as the

spleen is in the body, it exerts an inhibitory action on the respiratory centre and therefore the withdrawing of this influence is equivalent to an augmentation of thyroid activity on the nervous system. This deduction is supported by the fact that injection of a purified spleen extract produces a relative inhibition. The antagonistic balancing influence of thyroid and spleen is not restricted, by the way, to the nervous system; it also appears in the regulation of peripheral functions.

The influence of thyroid secretion on the higher levels of central nervous system activity was studied by quantitative investigations of the reflex response to stimulations with light or sound. We subject, for instance, the eye of a rabbit to light of which the intensity, distance from the eye and duration are exactly measured. After the threshold value for contraction of the pupil of the given normal animal has been determined, thyroxin is injected. If this is repeated two or three times, the threshold value for eliciting the reflex is found to be greatly decreased; consequently, the sensitivity of this mechanism is increased. Guinea pigs react precisely to a high pitched sound with a rapid movement of the ear. This reflex is an interesting instance contrary to a current notion that reflex activity is necessarily subject to fatigue. In reality this reflex appears to be in a high degree indefatigable. For, if the stimulus is repeated every second, the animal will respond without fail for an hour or more with the rapid jerk of its ears. The intensity of the stimulus is easily measured by the pressure which is necessary to drive the air through a Galton pipe for attaining the threshold intensity of sound. The distance of the pipe from the animal is kept constant. Again after increasing experimentally the thyroid secretion, the animal becomes far more sensitive to sound while thyroidectomy greatly depresses its sentitivity.

Even those parts of the brain to which we ascribe the highest functions, namely, the cortex of the forebrain, can experimentally be recognized as affected by the thyroid hormone. Narcosis by ether, as used in surgery to make operations painless for the patient, is mainly a temporary inhibition of the highest centers of the cerebral cortex; in human beings the seat of consciousness. If the thyroid hormone is capable of sensitizing the cortex, we should expect in states of hyper- and hypothyroidism a different reaction towards narcotics than in the normal state. This expectation is readily verified under the condition that a narcotic is administered by a method that allows a quantitative

estimation of the amount of narcotic substance necessary to produce narcosis under controlled conditions of application and time. The method we employed was to drive ether mixed with known amounts of air under constant pressure through stopcocks of graded dimensions and measuring the amount of ether used as soon as narcosis was attained. The latter value was remarkably constant for a given individual. Animals under the influence of increased thyroid hormone were far more resistant to narcosis than in the normal state. We should be justified to draw the conclusion that thyroid internal secretion raises the vitality of the higher parts of the brain, a conclusion, of course, not new to us, as intellectual deficiency is known to us from cretinism based on lack of thyroid activity.

At the present state of our knowledge the thyroid is outstanding in demonstrating the relation between nervous system and internal secretion. Less is known regarding the other glands of internal secretion, with the exception of the gonads. Loss of the latter does not alone extinguish the sexual functions, but also to a certain extent depresses the vivacity of certain of the nervous activities. What has frequently been viewed as a kind of rejuvenation is more probably a temporary reactivation of the nervous system by the introduction of appropriate sexual hormones. Perhaps if we are able to develop more refined methods to test the activity of the brain, we shall know more about the influence of the hypophysis and the adrenal glands on nervous activity, an influence which we are warranted to presume.

Notwithstanding the fact that glands with internal secretion are autonomic, a regulatory influence of the nervous system on their secretion must be postulated, as anatomy shows them to be richly inervated. Experimental investigation has given decisive proof of a regulatory nervous control of internal secretion. The evidence for the adrenal gland, insofar as adrenalin, the hormone of the medullary substance, is concerned, is clear cut. Stimulation of the splanchnic nerves, whether experimentally through induction currents or naturally by various reflexes, causes an output of adrenalin into the blood. Whenever through muscle work, or fear, rage and other emotions, greater demands are imposed on the organism, the central nervous system leads by natural impulses to a secretion of adrenalin. In this way, as Cannon ably has put it, the adrenal gland becomes one of the helpmates of the organism to overcome the stress and strain of life.

The frequency of diabetes has directed popular attention to the pancreas, which, by way of its islet cells produces insulin, the powerful regulator of carbohydrate metabolism. Previous to the discovery of insulin, my collaborator, Dr. de Corral from Madrid, showed that stimulation of the vagus nerve caused the level of blood sugar to become lowered, which is precisely, since we now know insulin, the reaction to increased secretion of this hormone. By employing more modern methods Zunz in Brussels has corroborated in a most convincing manner the nervous control of the regulation of carbohydrate metabolism by insulin.

The question of the nervous regulation of thyroid secretion was for a long time beset with peculiar difficulties. But they have been overcome since we have learned to use well-defined reactions of the thyroid internal secretion which take into consideration the time in which these reactions gradually develop. Absorption of fluid from the subcutaneous tissue of a lower extremity takes a certain time and it is of approximately the same duration whether the animal is in a cold or warm environment. This becomes different when the thyroid is denervated. The absorption time is then longer and an appreciable difference between cold and warmth appears. Evidently the regulation of absorption has become impaired. That this is exclusively due to the denervation of the thyroid is further demonstrated by the fact that the said difference is accentuated by thyroidectomy. Through the more refined method of thermoelectrical measurement of the temperature of the liver, we were able to show that after denervation of the thyroid, thermo-regulation in the liver as a response to cooling worked less efficiently and again that thyroidectomy magnified this inefficiency.

By way of the sympathetic nerves the intensity of the thyroid secretion is adjusted to the needs of the organism. I have before drawn attention to the influence of the thyroid secretion on the central nervous system. The influence just shown, in the reverse direction from the central nervous system on the thyroid, allows the suggestive inference, that central nervous system and thyroid are functionally linked together in shape of a circuit and that both are reciprocally interdependent. In consequence of this, when impulses from the nervous system stimulate thyroid secretion, the latter will lead to an increased activity of the nervous system and we shall see exactly as in the case of the heart, excitations incessantly going on in both direc-

tions, eventually leading to the diseased state of hyperthyroidism and nervous instability, until medical aid breaks the vicious circle.

It is appropriate to close my talk with the hypophysis, the remarkable gland at the base of the brain, unique in its dominating position over most of the glands with internal secretion and a ruler besides of important bodily functions of a general character. But even this powerful gland is subject to nervous regulation, emanating from pathways in the hypothalmus as recent fine work from American neurologists has demonstrated.

I thank the distinguished audience for the kind patience with which it has followed my lecture. It would be gratifying to have been in a little way successful in drawing a picture of the building up of life's regulation by nervous and hormonal control. Life shines out as a unity and as such is lavish in employment of means to its ends.

Entomological Terms

The standard work on entomological terminology published in 1906 and known as Smith's Glossary (Explanation of Terms Used in Entomology) has been completely revised and rewritten. The original volume contained about 4300 terms while the revision contains nearly 12,000 definitions. The science of entomology is a much broader field today than it was over thirty years ago when the original volume was written. The revision has brought up to date the modern as well as the original usage of terms, and includes terms from many related scientific fields. Some of these fields closely allied to entomology and concerned in the revised glossary are: chemistry, physics, botany, zoology, medicine and medical entomology. Various phases of these are also included such as cytology, physiology, genetics, ecology, morphology, embryology, development and taxonomy. A few mathematical terms are also included. Many of the terms are defined according to the commonly accepted usage. Special terms applicable to restricted groups are given and in such cases the originator of the term and his definition are given. There are two appendices, one of Latin abbreviations and the other of arbitrary signs and symbols used in entomology. Nine plates of various structures are included, three of which appeared in the original volume. A bibliography of the most important references is also included.

The revision represents an enormous amount of work on the part of the author. The book is well bound and printed on good quality paper in legible 10-point type. The binding is said to be of water-, dirt- and insect-proof cloth.

The new volume will serve as the standard reference book on terminology for entomology and closely related sciences for years to come. Every entomologist should have a copy to refer to before attempting to concoct some new term, or give a term now in use a new meaning.—R. H. Davidson.

A Glossary of Entomology (Smith's "An Explanation of Terms Used in Entomology") revised and rewritten, by J. R. de la Torre-Bueno. ix+336 pp. Brooklyn, N. Y., The Brooklyn Entomological Society, 1937. $5.00.

THE GASTROINTESTINAL HORMONES OR AUTACOIDS

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INTRODUCTION

It is an evident fact that bodily processes are subject to excitation and inhibition. The chief agencies through which the bodily processes are augmented and retarded, or controlled, are: (a) the nervous system and (b) the hormone or autacoid secreting cells or organs. Nerves may effect muscle tissue so that it contracts or relaxes, or secretory cells, such as the salivary glands, so that their rate of secretion increases or decreases. Hormones or autacoids also act to augment or to retard bodily processes.

The hormones have been called autacoids, meaning self-remedial substances, because they act much like drugs or remedial agents. It is believed that two sorts of autacoids exist functionally, the hormones (to excite), which augment bodily processes, and the chalones (to inhibit), which retard bodily processes.

The autacoids are secreted into the blood and/or lymph by glands without ducts, in contrast to such glands as the salivary glands, whose secretion is drained externally into the mouth by ducts. Hence, the terms "Ductless Glands" and "Glands of Internal Secretion" are applied to the autacoid producing glands. The expression "Endocrine Glands" is also used, the word "endocrine" meaning to separate within.

Since, in the gastrointestinal tract certain food substances excite the secretion of gastric and pancreatic juice, we refer to these substances as "secretagogues." Secretagogues are substances which are present in food or which arise from the digestion of food. They stimulate gastric and pancreatic secretion. As will be noted later secretagogues may excite secretion by acting locally on the lining or mucosa of the stomach and intestine or possibly by being absorbed into the blood stream. Secretagogues are not hormones, since they are not formed by the living cells of the body, but are present in or result from the digestion of food. Any blood borne or circulating agent stimulating or depressing bodily activities is called a "humoral

agent" whether it is a hormone or secretagogue, or substances of unknown nature.

SALIVARY GLANDS

All the evidence shows that the secretion of saliva is increased or decreased through a nervous mechanism. When food is placed in the mouth saliva flows because sensory nerve impulses pass to the brain and excite a salivary center (medulla), from which secretory nerve impulses pass to the salivary glands causing them to secrete. The contact of food with the oral mucosa does not cause the cells of the mucosa to secrete a hormone into the blood. For example, if lemon juice is placed in the mouth of a dog, saliva flows copiously. If the nerves to the salivary glands are cut one day and then lemon juice is applied to the mouth the next day, saliva is not formed. When extracts of the oral and pharyngeal mucosa are made and then injected intravenously or subcutaneously, the salivary glands are not stimulated.

The situation is different, however, in the case of the stomach, pancreas and liver. It is interesting that, whereas, the salivary glands appear to be controlled solely by nerves, the stomach is controlled by nerves and autacoids. Secretion of pancreatic juice and bile are controlled chiefly by autacoids and humoral (blood borne) agents. Nerves play a minor role in the formation of the latter two secretions.

GASTRIC SECRETION

The secretion of the acid gastric juice may be divided into three phases when one considers the point at which the stimuli are acting. These phases are (a) the cephalic phase, (b) the gastric phase, and (c) the intestinal phase. When food is seen, smelled or tasted in the presence of appetite, nerve impulses pass to the brain and then to the stomach by way of the vagus nerves causing the socalled "psychic" secretion of gastric juice. This phase is entirely nervous. The gastric phase is initiated by distension of the stomach and by the secretagogues in the food or the secretagogues produced by the gastric digestion of food. Whether distension of the stomach or the contact of secretagogues with the lining of the stomach excite secretion by stimulating the local enteric nervous system in the stomach wall or by causing a hormone to be produced is not known. Both may be concerned. It is known that secretagogues probably do not

act in the stomach by being absorbed (3). The intestinal phase of gastric secretion is initiated by secretagogues acting on the mucosa of the intestine. Whether they act by causing a hormone to be produced or by being absorbed into the blood is not certain. It is possible that they may act by being absorbed into the blood (3).

It has been established that a humoral mechanism (agents such as a hormone or secretagogues) for stimulating gastric secretion exists. This was first shown (1, 4) (Ivy and Farrell) by auto-transplanting a small pouch of the stomach beneath the skin. When such an animal is fed, the transplanted pouch secretes acid gastric juice. Hence, when the animal ate, some substance or substances passed into the blood which stimulated the transplanted pouch. Whether the humoral or blood borne substance is of the nature of a hormone or of the nature of secretagogues is not certain.

An acid, saline, or alcoholic extract of the mucosa of the pyloric portion of the stomach, when injected subcutaneously, stimulates gastric secretion. The active principle of such extracts is called gastrin or the gastric hormone. Histamine in crystalline form has been isolated from such extracts, and the evidence indicates that histamine is the sole secretory excitant in such extracts (5). It cannot be concluded, however, that histamine is the gastric hormone, (a) because it has not been shown clearly that the histamine content of the blood increases after eating, and (b) because it has been reported that a substance has been dialyzed from the blood of a fed animal which on subcutaneous injection stimulates gastric secretion but does not depress blood pressure on intravenous injection like histamine.

Histamine is now frequently used in man to test the ability of the stomach to secrete acid.

PANCREATIC SECRETION

It is known that nerves are present in the vagus nerve trunks which excite and inhibit the formation of pancreatic secretion. Nerve fibers are present in the splanchnic nerve trunks which when stimulated cause a decrease in blood flow to the pancreas and a decrease in the formation of pancreatic juice. A "psychic" secretion of pancreatic juice occurs, but is relatively small in volume (5–10 cc., rarely more).

The principle mechanism which has been demonstrated to exist for the stimulation of pancreatic secretion when a meal is ingested is the elaboration of the hormone secretin. This hormone is produced when dilute acids, fatty acids, soaps and peptones contact the upper intestinal mucosa.

The discovery of this hormone by Bayliss and Starling in 1902 constitutes one of the major historical events in the field of Endocrinology. To stimulating principles, such as secretin, Starling (7) applied the term, hormone. The essential observations made by Bayliss and Starling were as follows: It had been known for sometime that dilute acid applied to the duodenal mucosa would cause the pancreas to secrete. This secretion was thought to be excited by a nervous reflex, and Bayliss and Starling desired to test this theory. They found that application of acid to the duodenum after the nerves to the pancreas had been sectioned still caused the gland to secrete, and that acid injected intravenously did not. They then made acid extracts of the duodenum and found that such extracts on intravenous injection stimulated the pancreas to secrete. It was then shown that when the circulation of two dogs was connected and acid placed into the duodenum of one, the pancreas of both secreted. Later it was shown that acid applied to an autotransplanted loop of intestine caused an autotransplanted portion of the pancreas to secrete (8). The possibility that secretagogues, after being absorbed into the blood, stimulate the pancreas, has been shown to be improbable (8a).

Purified preparations of secretin have been injected into normal human subjects (9). The secretion of the pancreas was, of course, stimulated. Secretin has apparently been crystallized (10); secretin crystals have also been prepared in the author's laboratory (11). From 0.016–0.008 mg. of the secretin base, from which crystals of secretin picrolonate were made, is adequate to stimulate the pancreas of dogs.

It is of interest that crystalline secretin stimulates the liver to secrete bile (12). The crucial experiment proving this was performed on animals deprived of their pancreas and gastrointestinal tract, so that the increase in flow of bile could not be secondary to increased activity of the pancreas and intestine. The cholagogue action of secretin, however, is not as marked as that of bile salts.

GALL BLADDER

Nerves pass to the gallbladder, but when stimulated only a small and variable amount of contraction occurs. It now appears to be established that the hormone cholecystokinin is the chief cause of gallbladder contraction and evacuation. This hormone is produced when dilute acids and fatty acids contact the duodenal mucosa. The essential facts demonstrating the existence of such a hormone are as follows: Extracts of duodenal mucosa have been made and injected into human and canine subjects; the gallbladder contracted and evacuated. Further, if the circulation of two dogs is connected and acid is placed in the duodenum of one, the gallbladder of both animals will contract. The intravenous injection of acid or of finely emulsified fat or chyle does not cause the gallbladder to contract. This shows that the absorption of acid or the products of the digestion of fat do not act as humoral agents for gallbladder contraction and evacuation.

This hormone is closely related to secretin chemically; but the two may be separated by an appropriate chemical procedure (12a).

ENTEROGASTRONE

Neutral fat inhibits gastric secretion and motility. This has been known for many years. It was formerly believed, however, that when fat contacted the stomach and duodenum the gastric activities were reduced by a nervous reflex. We now know that this inhibitory action of fat is due to the chalone enterogastrone, although the possibility that nerves are also concerned has not been entirely ruled out.

The essential facts showing that enterogastrone exists are as follows: When a small pouch of the stomach is transplanted beneath the skin and a balloon is inserted into the pouch so as to record its movement, it is found that the movements are markedly diminished a few minutes after fat is placed into the duodenum (13). The same is true for the acid secretion of the transplanted pouch (14). A concentrated solution of glucose or cane sugar acts similarly to fat. Gastric secretion and motility are not inhibited when finely emulsified fat or chyle is injected intravenously. This shows that it is not the absorbed food fat circulating in the blood that causes the inhibition of the movements and secretion of the pouch. Hence, the inhibition must

be due to some specific substance or chalone secreted by the duodenal mucosa into the blood. Further, extracts of duodenal mucosa have been made which, when injected intravenously or subcutaneously, inhibit gastric secretion and motility (21).

The enterogastrone preparations made to date are not toxic, but they are not sufficiently "pure" to use in man. When the chalone has been prepared in a sufficiently "pure" or concentrated form, it may prove to be of value in the management of patients with "peptic" ulcer.

OTHER GASTRO-INTESTINAL HORMONES

Incretin: Rather strong presumptive evidence indicates that the duodenal mucosa produces a hormone which stimulates the islet cells of the pancreas to secrete insulin (1). It also appears to have a direct hypoglycemic property, since it lowers the blood sugar level in depancreatized animals (15, 16).

Enterocrinin, the hormone for the stimulation of intestinal secretion: When one observes the secretion of a loop of intestine which has been transplanted beneath the skin, it is noted that a copious flow of intestinal juice from this loop does not occur after feeding the animal (17). Closer study, however, indicates that some increase in the volume of secretion and output of enzymes occurs (18). A preparation of the intestinal mucosa has now been made free of blood pressure depressing substances which on injection increases the formation of intestinal juice. This hormone is called enterocrinin (Nasset).

Enterocin, the gastro-intestinal motor hormone: The possible existence of a hormone produced by the intestinal mucosa which augments gastro-intestinal tone and motility during digestion has been suggested by a number of observers (1). Although the motility of a transplanted loop of intestine is not definitely increased after the ingestion of a meal, closer analysis may show that it is. Preparations (1) of intestinal mucosa have been made which on injection augment intestinal motility (19). The active principle (the author calls this principle enterocin) has certain chemical properties related to secretin, but is not identical with it (20). It is not related to acetyl choline because its motore effect is not antagonized by atropine.

Concerning an erythropoietic hormone, it has been suggested that the gastrointestinal mucosa produces a hormone which is related to erythropoiesis. Little or no evidence exists to substantiate such a suggestion. The *desiccated* stomach, duodenum

and colon of the pig is active in the management of pernicious anemia. But, this is probably due to the presence of an enzyme (intrinsic factor of Castle) which reacts with substances in the cells of the gut wall to produce the active erthropoietic substance. During life it is believed that the enzyme is secreted into the gastric and intestinal juice, and acts on certain foods, such as meat, to produce a substance which is absorbed into the blood and is used by the bone marrow to produce erythrocytes.

SUMMARY

From this brief review it is clear that the mucosa of the gastrointestinal tract is a veritable storehouse of autacoids. Seven or more hormones may be produced. The existence of three, namely, secretin cholecystokinin and enterogastrone, may be considered as established. The evidence is strongly presumptive for the existence of three others, namely, gastrin, incretin, and enterocrinin. Good physiological evidence for the existence of enterocin has not been produced.

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THE PROLONGATION OF INSULIN ACTION

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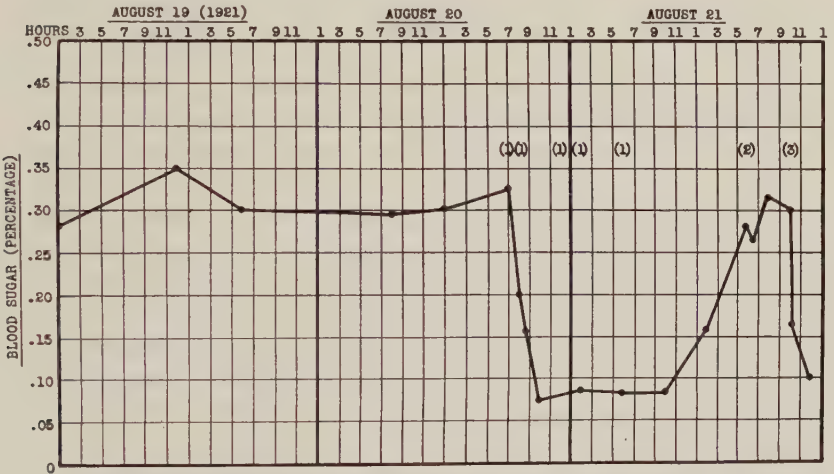
As an introduction to the consideration of the different forms of insulin, which will be discussed later, a few remarks may be made about the anti-diabetic material which was available in 1921. The administration of an effective dose of this material caused a fairly prompt fall of the blood sugar to a low level. The action was maintained for an appreciable length of time (Fig. 1). It is readily apparent to physiologists, who have worked with various preparations of insulin, that the crude material available 16 years ago had a much more prolonged action than the more highly purified preparations. While there is considerable difficulty in making an accurate comparison of materials used in 1922 and, let us say, in 1930, many clinicians also agree that the crude preparations exerted a much more prolonged effect than the solutions of the purified insulin. The removal of impurities decreased the incidence of local reactions at the site of the injection but did not improve insulin as a specific therapeutic agent.

Insulin was available in a very satisfactory state of purity before the substance was isolated in crystalline form. The preparation of the crystals was, from the chemical viewpoint, an extremely important landmark in the history of the development of the subject. This was accomplished by Abel, Geiling, Rouiller, Bell and Wintersteiner in 1927. The crystals occur in several forms and are to some extent interconvertible. The recent work of my colleague, D. A. Scott (1935, 1936), on the rôle of zinc in the crystallization of insulin has placed the preparation of these crystals on a more scientific basis. It is now a relatively easy matter to obtain large amounts and a fair yield (75 per cent or higher) from suitable amorphous material. The crystalline material was termed by Scott "zinc insulinate." Other metals may also be used in the preparation of the crystals and these combine with insulin in amounts which are proportional to their atomic weight. The average ash content of each insulin salt is proportional to the atomic weight of the metal it contains. This indicates that the crystals contain the metals as chemically combined constituents and not as impurities. Scott

and Fisher (1935) have found that if the molecular weight of insulin be taken as 20,000 each formula weight of insulin combines with 1.4 formula weights of cadmium, with 1.5 formula weights of cobalt and 1.6 formula weights of zinc. If the molecular weight of insulin should be 40,000 one formula weight would therefore combine with approximately three formula weights of the metals. Svedberg, using his ultracentrifuge technique, has suggested 35,100 for the molecular weight of insulin and Crowfoot, on the basis of X-ray studies, a value of 37,200.



Effect of insulin on the blood sugar curve of a depancreatized dog (redrawn from Banting and Best). (1) Injection of extract of degenerated pancreas; (2) extract after incubation with pancreatic juice; (3) extract incubated without pancreatic juice. Blood sugars by Myers-Bailey modification of Lewis-Benedict method.

FIGURE 1

The chemical structure of these crystals of insulin has attracted a great deal of attention. This is not surprising since there are relatively few crystalline proteins which can be so readily assayed. An appropriate idea of the potency can be obtained when only a few milligrams of the material are available. There is an abundance of evidence that the crystalline material is protein in nature. Eight amino acids have also been isolated—cystine, tyrosine, arginine, histidine, lysine, leucine, glutamic acid and phenylalanine. Others are quite likely present. In the search for the active groupings in the molecule attention has been directed at the NH_2 group and the disulphide linkages. Destruction of the amino group irreversibly inactivates insulin. When the disulphide grouping is reduced to the

sulphydryl the specific activity is lost—some investigators believe irreversibly while others think that a partial inactivation which can be reversed may be produced. An insulin-plastein may be formed when the products of peptic digestion of insulin are allowed to interact under certain conditions but this, as Scott considered likely before he performed the experiment, possessed no anti-diabetic activity. The complexity of the insulin molecule makes the possibility of synthesis remote.

The international yardstick for insulin is the new crystalline standard. Fifty grams of crystals were prepared in the Connaught Laboratories by Dr. Scott and presented to the Health Organization of the League of Nations by the Insulin Committee of the University of Toronto. The potency of the new standard was compared to that of the old amorphous preparation in a number of laboratories. The results were submitted to representatives of the National Institute for Medical Research, the University of Copenhagen and the University of Toronto (represented by Sir Henry Dale, Professor August Krogh and the writer). A recommendation was made that a value of 22 units per mg. be assigned to this new standard. It was felt that this would not change the strength of the unit. This recommendation was accepted by the Health Organization of the League of Nations (1936). The unit of insulin is, therefore, defined as the activity contained in $\frac{1}{22}$ of a mg. (0.045 mg.) of the new International Standard.

IMPROVING INSULIN AS A THERAPEUTIC AGENT

The advances recently made in this field have prompted me to discuss it in some detail.

Various efforts were made in 1922 and 1923 to find a means of administering insulin by the enteral route. Very little success was secured, and if we now take all the reports on this problem into account, the situation is approximately as follows: Insulin is destroyed by the enzymes of the stomach and small intestine. Small amounts of insulin may be absorbed from the small intestine, particularly in young animals when very large doses are given. The rate of absorption is not predictable. There is no appreciable absorption from the large intestine. The situation with respect to the absorption of insulin from other mucous membranes is not more promising. An anti-diabetic effect can be observed when an insulin solution is inhaled, but results of practical value have not been secured. A very little insulin

may be absorbed through the skin when vigorously rubbed in with a lanoline base.

It is well known that the anti-diabetic hormone is rapidly absorbed when given intraperitoneally, intramuscularly or subcutaneously. The rate of action of purified insulin is only slightly less when given subcutaneously than when administered into a vein, and intramuscular injection does not appreciably delay absorption. We can, therefore, restrict our discussion very largely to the question of modification of the rate of action of insulin which is administered subcutaneously.

As stated above there is an abundance of evidence to show that crude insulin exerts a more prolonged effect than the purified material. It is also well established that a given amount of insulin administered in several small doses exerts a greater effect than when the same amount is administered in large doses. This effect is due, probably, to the relatively large amount of insulin excreted or destroyed when the large doses are employed. These facts have stimulated investigators to attempt to secure the prolongation of the absorption of insulin from the subcutaneous tissue spaces. The first report of an attempt to do this was that of Burgess, Campbell, Osman, Payne and Poulton (1923), who used insulin in gum arabic solutions. These investigators secured a definite prolongation of insulin action in diabetic patients and in experimental animals. Similar results were obtained by de Jongh and Laqueur (1925). Leyton (1929) convinced himself of the efficiency of insulin solutions mixed with certain oils. He was able to give larger doses, and apparently expected the use of oily suspensions of insulin to become general. Surányi and Szalai (1930) obtained a prolonged action and less frequent hypoglycaemic reactions when insulin was mixed with lecithin emulsions. Skouge and Schrumpf (1932) confirmed the lecithin results and found, as might perhaps be expected, that no extension of the insulin effect was obtained when the mixtures were given intravenously. They found it possible to administer subcutaneously large doses of insulin in lecithin without the production of hypoglycaemic reactions. Several groups of investigators—Wermer and Monguió (1933) and Clausen (1934)—attempted to prolong the action of insulin by administering pituitrin or epinephrin with the insulin solution. Little success attended these efforts.

Apparently the first attempt to modify the action of insulin by the use of metals was that of Bertrand and Mâcheboeuf

(1926). These investigators reported a very definite extension of insulin action when cobalt and nickel were added to the insulin solutions. This report led to the development of a controversy, and the findings have not been generally confirmed. We must not lose sight of the fact, however, that Bertrand and his collaborator were the first to suggest the use of a metal in this connection. The blood sugar curves which Maxwell and Bischoff (1935) have published appear to indicate that basic ferric chloride definitely slows the absorption of insulin. These investigators have used other metals including zinc in their studies of other hormones.

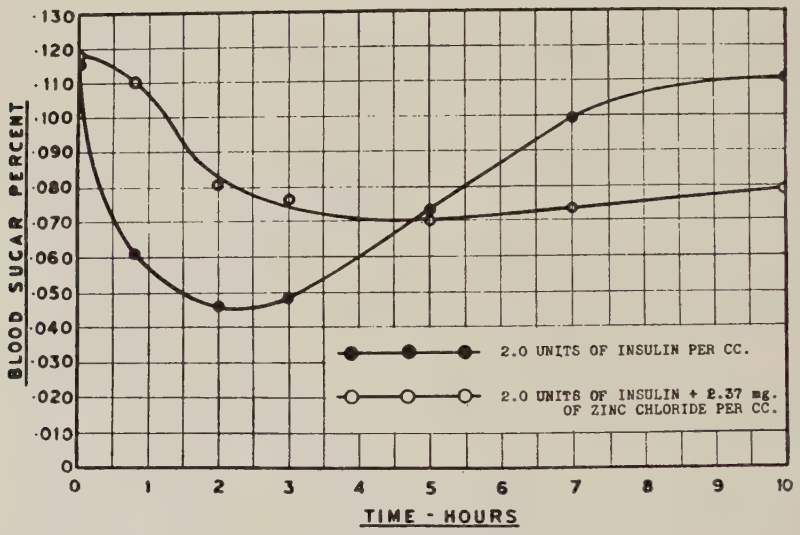


FIGURE 2. (From Scott and Fisher.)

Scott and Fisher were led to a study of the action of zinc salts on the rate of absorption of insulin by the findings referred to above, that zinc, or some closely related metal, was an essential component of crystalline insulin. The addition of the appropriate amount of zinc to insulin solution definitely delays the absorption of insulin. It is possible that the zinc forms a compound between the insulin and some component of the tissues, or that the zinc solution delays the absorption of the insulin by an astringent action or by some other mechanism. Scott and Fisher have reported very definite findings in rabbits (Fig. 2), and Dr. Kerr, working under my general direction, has confirmed their findings in the dog (Fig. 3). Dr. Walter Camp-

bell in Toronto and Dr. Rabinowitch in Montreal have recently used zinc insulin in diabetic patients. A prolonged insulin effect has been observed.

PROTAMINE INSULIN

This brings us to a consideration of protamine insulin which has been used with very considerable success for more than two years by Hagedorn (1936) and his colleagues in Copenhagen. The chemical background of this ingenious procedure for delaying the absorption of insulin is most interesting and I will now digress for a moment to discuss it.

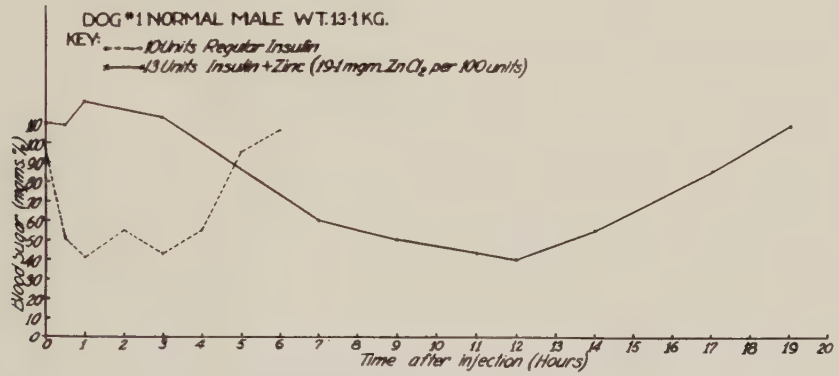

DOG #1 NORMAL MALE WT. 13·1 KG.
KEY: ----10 Units Regular Insulin
——13 Units Insulin + Zinc (19·1 mgm. $ZnCl_2$ per 100 units)
Blood Sugar (mgms. %)
Time after injection (Hours)

FIGURE 3. (From Kerr and Best.)

In 1868 Friedrich Miescher began an investigation of the chemistry of cell nuclei. This work, conducted in Hoppe-Seyler's laboratory, showed that proteins of acidic character containing phosphoric acid were present in nuclei of pus cells. Later he found these nuclions of nucleic acids in combination with basic substances in the sperm of salmon. He named the basic substances protamines. Some sixteen years later Kossel detected another type of basic substance in combination with nucleic acid. These were later shown to be similar to but somewhat more complex than the protamines. They are now called the histones. Kossel also isolated a protamine from the sperm of the sturgeon, which resembled but was not identical with the base from salmon sperm. Protamine was adopted as the general name for these bases while each separate one was called after the family name of the fish from which it was secured—thus sturine (sturgeon) etc. This protamine contains arginine, lysine

and histidine, and is one of the triprotamines. Sturine also contains alanine and leucine. Clupeine obtained from herring sperm is a monoprotamine and contains arginine as the only basic constituent. Alanine, serine, an aminovaleric acid, and proline were also present. Salmine is also a monoprotamine and contains serine, aminovaleric acid and proline as well as arginine. Hagedorn and his colleagues have prepared a new protamine—probably of the mono- variety—from the sperm of Salmo irideus (salmiridine) and they have used this in their clinical experiments, with protamine insulin.

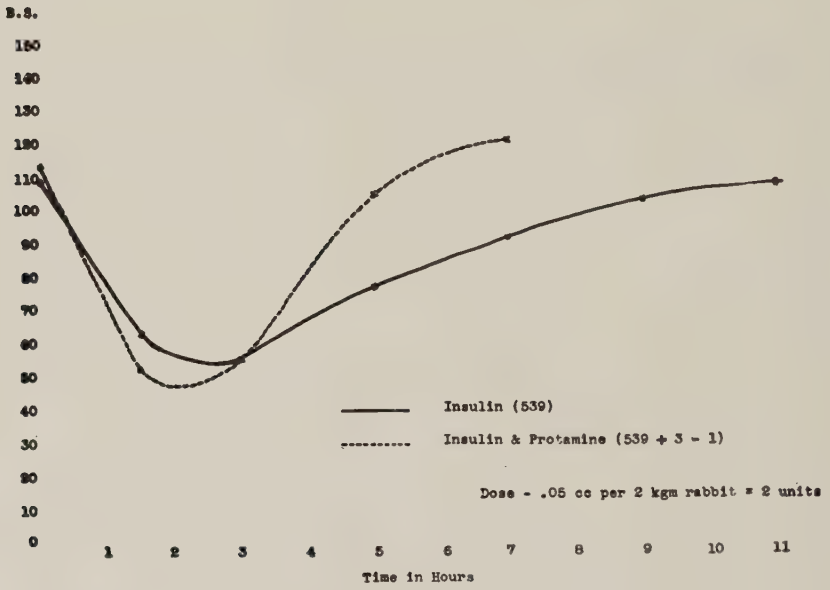


FIGURE 4. (From Scott and Fisher.)

Proteins are known to combine with the so-called protamines. The compounds are soluble at a certain hydrogen ion concentration, but insoluble at others. Hagedorn and his collaborators have very ingeniously taken advantage of this fact and have demonstrated beyond doubt that the compound of insulin and protamine is a very effective therapeutic agent in certain cases. A clear solution of protamine is added to insulin. The protamine is dissolved in a buffer solution of such a composition that the hydrogen ion concentration of the insulin-protamine mixture is approximately pH 7.2. At this pH the insulin-

protamine compound is insoluble and forms a flocculent precipitate. If the vial containing the mixture is shaken and the suspension administered, the insulin is slowly liberated in the tissues and a prolonged anti-diabetic effect is exerted. That this is due to slow absorption has been demonstrated directly by Beecher and Krogh (1936) who watched the rate of disappearance of regular and protamine insulin from the tissue spaces. The effect of protamine insulin on rabbits or dogs is easily demonstrated (Figs. 4 and 5).

It has now been agreed by most diabetic specialists that protamine insulin has certain advantages over regular insulin in many cases of diabetes. The advantages are as follows:

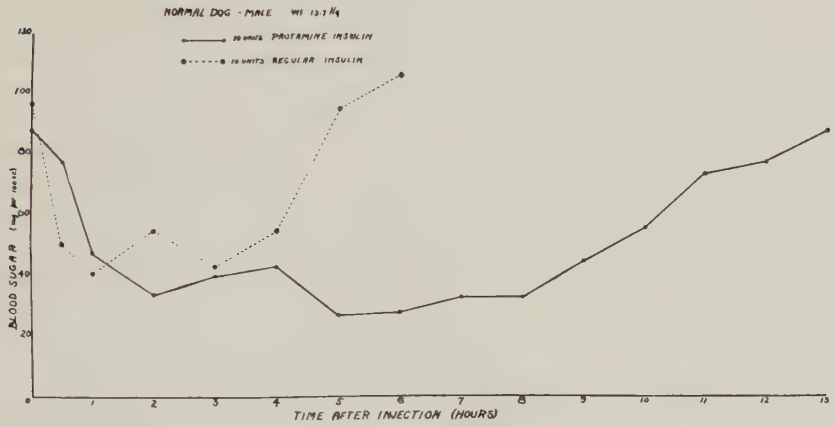


FIGURE 5. (From Kerr and Best.)

(1) The duration of the anti-diabetic effect is longer with protamine insulin than with the regular product. The number of injections required is, therefore, reduced. (2) The blood sugar curve is more regular and does not show the high peaks and marked depressions which are often observed with the regular material. (3) The ketosis is reduced when protamine insulin is used. (4) There are fewer hypoglycaemic reactions. (5) The patients feel better.

ZINC AND PROTAMINE INSULIN

When the protamine solution is mixed with the insulin and the insoluble precipitate formed, the resulting suspension of protamine insulin is not stable indefinitely. It has been found in the Connaught Laboratories and in the Insulin Committee's

testing department that in some cases after a few days a portion of the material sticks to the sides of the glass vial (Fig. 6) and that it is impossible to secure samples of uniform potency. It has been found by Scott and Fisher that this situation is corrected by the addition of a small amount of zinc to the protamine insulin mixture. The zinc in some way stabilizes the suspension and prevents it sticking to the glass vial. If this were the only effect of zinc it would be a very significant contribution but there are grounds for belief that zinc plays a rôle in the formation of a protamine insulin compound. Thus Scott and Fisher showed (1936) that when preparations of insulin and protamine from which inorganic material has been in large part removed were mixed a prolonged anti-diabetic effect was not secured. If, however, a small amount of zinc was present in this mixture, a slow absorption of insulin and a prolonged action were consistently produced. These results on rabbits have been confirmed by Kerr and Best (1937) on dogs. (Fig. 7). This compound of protamine and insulin to which zinc has been added has been named by the Toronto group "protamine zinc insulin." The use of zinc has made it possible to distribute the preparation in one vial. The suspension is stable for at least six months and perhaps for much longer periods of time. The protamine used in the Connaught Laboratories has been prepared from the mature testes of several species of British Columbia salmon, namely, spring salmon (Oncorhynchus tschawytscha), cohoe salmon (Oncorhyncus kisutch) and the steelhead (Salmo gairdneri). These products are quite as satisfactory as those secured from rainbow trout (Salmo irideus) and are readily available in large quantities.

"FREE INSULIN" IN THE PROTAMINE ZINC INSULIN MIXTURE

Some clinicians have raised objections to the use of protamine insulin and protamine zinc insulin on the grounds that they do not exert their effects with sufficient rapidity. This has been overcome by the administration of a small amount of regular insulin with the protamine zinc insulin mixture. Quite recently a preparation, made by Fisher and Scott, which contains in addition to protamine zinc insulin a certain proportion of "free insulin," has been tested by Kerr and McCutcheon under my general direction in the Department of Physiology. It has been found that a rapid effect comparable to that obtained with regular insulin is secured and, further, that a prolonged

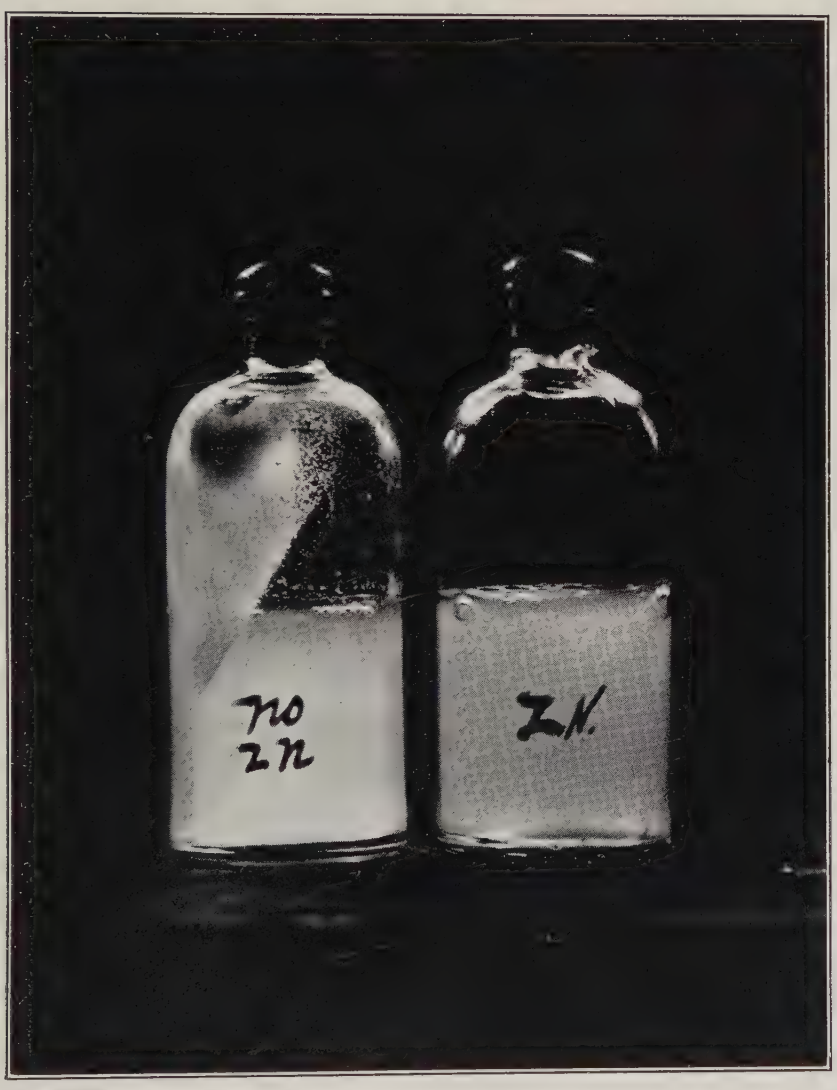
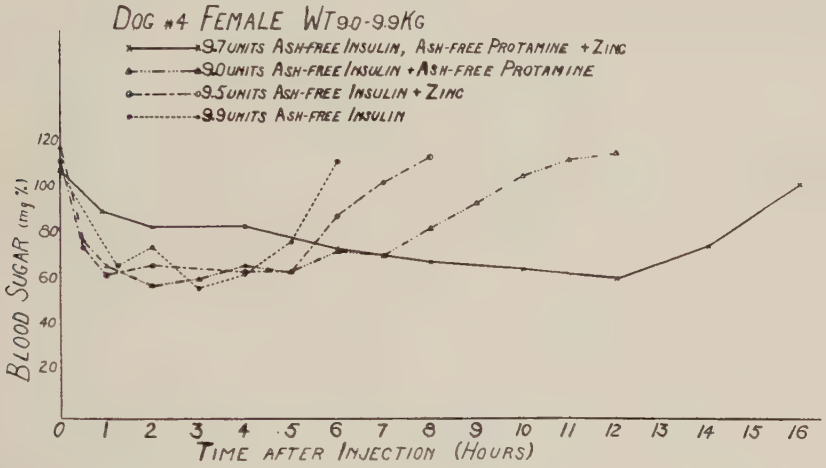


FIGURE 6

action is also produced (Fig. 8). There are some difficulties to be solved before a preparation of this kind suitable for clinical use can be made but it seems probable that a mixture which


DOG #4 FEMALE WT 9.0-9.9 KG
9.7 UNITS ASH-FREE INSULIN, ASH-FREE PROTAMINE + ZINC
9.0 UNITS ASH-FREE INSULIN + ASH-FREE PROTAMINE
9.5 UNITS ASH-FREE INSULIN + ZINC
9.9 UNITS ASH-FREE INSULIN
BLOOD SUGAR (mg %)
120
100
80
60
40
20
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
TIME AFTER INJECTION (HOURS)

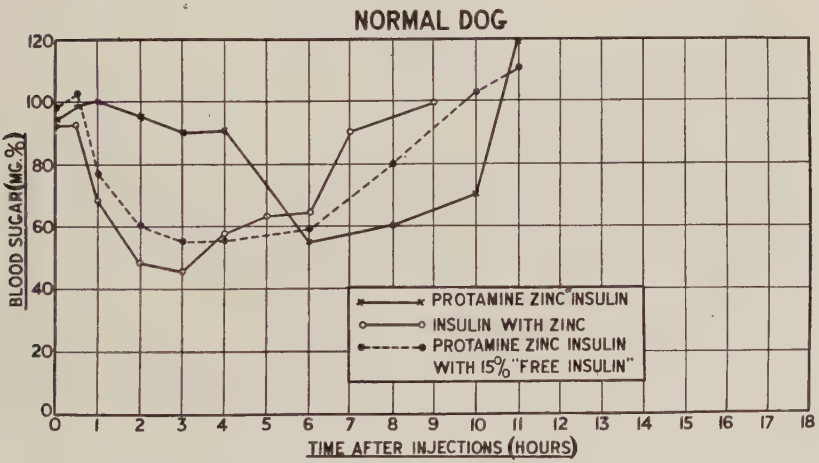


FIGURE 7 (upper); FIGURE 8 (lower), both from Kerr and Best.

will produce a rapid anti-diabetic effect and also a prolonged one, will, in due course, be made available. Clinical trial of this mixture is now being made.

PROTAMINE INSULIN IN DEPANCREATIZED DOGS

While the use of protamine insulin in diabetic patients had been investigated in some detail before these experiments on dogs were initiated considerable interest is attached to the findings in a completely depancreatized animal. Dr. Kerr has found it possible to keep several of the members of our colony of diabetic dogs in an excellent state of health and on a very liberal diet with one dose of protamine or protamine zinc insulin daily—20 units approximately for a 10 kilogram dog. The animals excrete only small amounts of sugar of the same order that are observed with two doses of regular insulin. When the daily

TABLE I

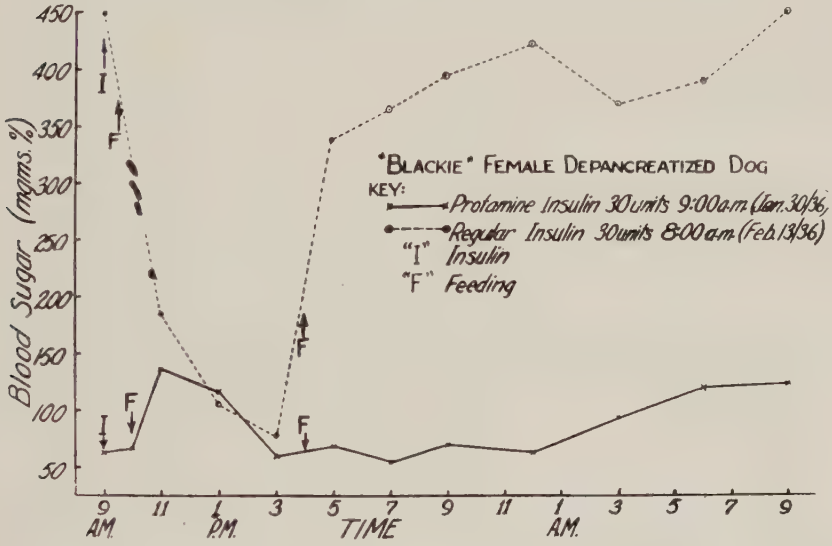
Dog	Regular Insulin		Protamine Insulin	
	Dose of Insulin	Sugar Excretion (Daily average 7 days)	Dose of Insulin	Sugar Excretion (Daily average 7 days)
"M"	17 units (q. a. m.)	40.9 g.	17 units (q. a. m.)	1.0 g.
"R"	26 units (q. a. m.)	13.2 g.	26 units (q. a. m.)	1.7 g.
"P"	34 units (q. a. m.)	56.1 g.	34 units (q. a. m.)	5.6 g.
"B"	30 units (q. a. m.)	48.3 g.	30 units (q. a. m.)	2.7 g.

dose of regular insulin (20 units) is given at one injection large amounts of sugar are excreted (Table 1, Kerr and Best). These results provide additional evidence that a large part of the insulin administered is excreted or otherwise lost when its absorption is very rapid. As in human patients the fluctuations of blood sugar throughout the day are largely eliminated and the incidence of hypoglycaemic reactions is very definitely less (Figs. 9 and 10). The results on diabetic dogs indicate that protamine insulin is a much more effective therapeutic agent than regular insulin.

HYPOGLYCAEMIA AFTER INJECTIONS OF PROTAMINE INSULIN

Observations on diabetic dogs have shown, in confirmation of clinical findings, that while the incidence of hypoglycaemic reactions is less with protamine insulin than with regular insulin those produced by the protamine preparations are often much more severe. No difficulties are encountered when the hypo-

glycaemia is treated immediately and plenty of sugar is made available. It is apparent that the hypoglycaemia produced by protamine insulin is more insidious in onset and, perhaps for this



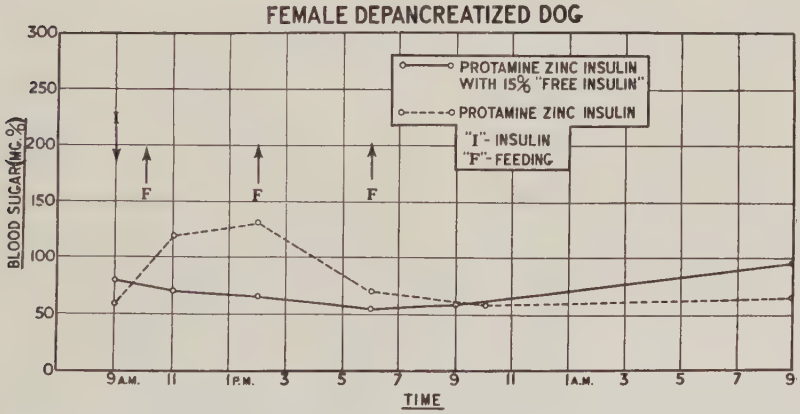


FIGURE 9 (upper); FIGURE 10 (lower), both from Kerr and Best.

reason, more difficult to correct than that produced by unmodified insulin. These findings emphasize the point that great care should be taken to prevent hypoglycaemia when protamine insulin or protamine zinc insulin is used.

DIET AND PROTAMINE INSULIN COMPOUND

Since the effect of one injection of protamine zinc insulin may persist for from 24 to 30 hours one dose per day may provide adequate insulin therapy in many clinical cases. This is the objective which most clinicians have in view. Since this preparation contains no appreciable amount of "free insulin" the rapid utilization of sugar very soon after administration, which is a characteristic effect of regular insulin, is not usually observed. Furthermore, the time after injection at which the lowest level of blood sugar is secured is much later than with unmodified insulin. For these reasons clinicians have found it necessary to make a redistribution of the food intake to provide larger amounts of carbohydrate later in the day. By this procedure a greater utilization of carbohydrate is secured and the incidence of the late hypoglycaemic reactions is decreased. The reader is referred to the clinical literature for details of the methods used.

SUMMARY

The results of Danish workers have made available a compound of insulin and protamine which exerts a prolonged anti-diabetic effect in cases of diabetes mellitus. Investigations initiated in the University of Toronto have shown that zinc may play an important rôle (1) in the stabilization of the protamine insulin compound and (2) in further prolonging the absorption of insulin. As a result of this series of studies a protamine zinc insulin preparation of satisfactory potency and stability, and contained in one vial, was made available for clinical trial. This product has been tested in many diabetic clinics and is now generally used. It is possible that this preparation may be further improved by the provision of a fixed amount of "free insulin" in the mixture. Some of the problems arising out of the use of these materials have been discussed.

Protamine insulin and protamine zinc insulin by enabling clinical and laboratory investigators to procure a more uniform and prolonged absorption of the anti-diabetic substance may assist materially in the investigation of many problems in carbohydrate metabolism.

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Recent Advances in Entomology

The revised second edition of "Recent Advances in Entomology," by A. D. Imms, gives promise of being as useful and as valuable a book for the next few years as the first edition has been since its appearance in 1931. The first edition was welcomed by all entomologists, particularly teachers, advanced graduate students and investigators.

The new edition is easy to read and summarizes in a very satisfactory manner the recent advances made in morphology, metamorphosis (including hormones), paleontology, sense organs and reflex behavior (visual stimuli in particular), coloration, ecology (including biological races and phase problems), and biological control. Some of the chapters have been revised considerably. The second edition has 56 new pages of text matter including some 27 new illustrations. The literature cited is presented in abbreviated form after the chapters discussing the topics named above.

The second edition should be found in all scientific libraries used by entomologists. It will also make a valuable addition to a personal library.

—Alvah Peterson.

Recent Advances in Entomology, 2nd edition, by A. D. Imms. 435 pages. Philadelphia, P. Blakiston's Son and Co., 1937. $5.00.

THE MALE SEX HORMONE

Some Factors Controlling Its Production and Some of Its Effects on the Reproductive Organs

WARREN O. NELSON
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That the testis has a function other than the production of spermatozoa has been known for many years. Indeed, the first experimental demonstration of endocrine activity for any organ occurred in 1849 when Berthold transplanted testes in the male fowl and observed that the usual external effects of castration did not occur in the bird bearing a transplanted gonad. Berthold's work has been confirmed repeatedly and, indeed, the effect of testicular hormone on the comb is at this time the basis of the principle method employed in gauging the activity of male hormone preparations. Complete accounts of the effects of testicular hormone upon the plumage and head furnishings of birds are given by Moore (1932) and Domm, Gustavson and Juhn (1932). Moore (1932) Witschi (1932) and Willier (1932) have adequately considered the question for lower animal forms as well as the embryological relations.

Berthold's observations on the relation of the testis to secondary sex characters in the fowl were eventually applied to mammals and it is now known that the normal function of the sex-accessory organs, viz., the seminal vesicle, prostate, epididymis, and Cowper's glands, depend upon the internal secretion of the testis. Furthermore, there is excellent evidence for the existence of a testis-hormone control over physiological maturation of the spermatozoa. Morphologically, the sperm are, apparently at least, mature when they are released from the testis into the epididymis. However, such sperm have a low capacity for fertilization. After a period of time spent in the epididymis under the influence of the male hormone their fertility is enhanced. This period of residence in the epididymis is looked upon as one during which physiological maturation occurs.

We, therefore, recognize the profound influence exerted over a group of reproductive organs by the internal secretion of the testis. However the testis itself is under the immediate control

of another endocrine organ, the anterior pituitary. This minute gland is believed to secrete two hormones which influence the activity of the male gonad. One of these is concerned with the stimulation of spermatogenesis and seems to be identical with the hormone that effects follicular growth in the ovary. The identity of the second hormone, which is involved in the stimulation of the interstitial cells and consequently with the production of male hormone, is less certain. Wallen-Lawrence, and Hisaw and his collaborators have presented evidence that would associate it with the pituitary hormone which stimulates luteinization in the ovary. More recently Evans, Simpson and Pencharz have suggested that a separate hormone, the interstitial cell-stimulating hormone, is the active factor. Regardless of which of these is the hormone actually involved in the stimulation of the interstitial cells it is possible to induce, selectively, either spermatogenesis or male hormone secretion in suitable test animals. The subject used in these studies is usually the hypophysectomized rat since the action of the hormone in question may be studied in the absence of any complications which might be introduced by the animal's own pituitary.

There are other influences which are important in normal testicular function. Such dietary factors as deficiencies in Vitamines A and E and in the mineral manganese have all been shown to result in sterility. The male hormone secretion of the testis is apparently not appreciably altered by these deficiencies since the sex-accessory organs have been reported by most workers to be normal. A somewhat different condition is observed in rats on a vitamine B-deficient or an inanition diet. Such animals have testes which show apparently normal spermatogenic activity, but which have a damaged endocrine function.

Thyroidectomy in young animals impairs both the spermatogenic and endocrine functions of the testis. The damage is much less severe in the adult animal. Hyperthyroidism, induced by the repeated administration of thyroid substance, results in a profound decrease in testis size. Microscopical examination of the sex organs of hyperthyroid animals reveals the loss of both the spermatogenic and endocrine functions of the testis. The exact mechanism involved in the testis damage induced by either hypo- or hyperthyroidism is not known, but it seems probable that the anterior pituitary is involved since profound histological changes are present in the hypophyses of such

animals. In the case of hyperthyroidism the possibility that the increased metabolic rate is a deterrent to normal testicular function cannot be disregarded. Febrile conditions, generally, damage the testis. The factor involved here probably is the increased temperature to which the testis is subjected.

Related to the condition seen in the testes of animals in febrile states is the histological picture observed in the cryptorchid testis. Observations dating back to Sir Astley Cooper in 1830 and more recently emphasized by Crew and Moore have indicated that the scrotum, through its capacity for heat loss, exercises an important influence in mammalian spermatogenesis. The lower, by several degrees Centigrade, temperature of the scrotum is exceedingly important for normal spermatogenesis in mammals (whales, rhinoceroses, elephants, and cetaceans are exceptions). Thus failure of the testis to descend into the scrotum from the abdomen or its replacement, by surgical procedures, into the abdomen does not permit the production of sperm. If a testis which is producing sperm is confined by surgical procedures spermatogenesis is halted. The degenerative changes which occur are in the inverse order of spermatogenesis, i. e., the spermatozoa are lost first with the spermatids, spermatocytes, and spermatogonia following in that order. The spermatogonia are relatively very resistant and it is usually very difficult to be certain that a few are not present even after many months. Perhaps the only procedure that will give definite evidence concerning the survival of spermatogonia is the replacement of the testis in the scrotum. Surviving germ cells will permit the resumption of spermatogenic activity.

It is commonly supposed that only the germinal elements of the testis are impaired when the organ is subjected to the condition of cryptorchidy. Thus it is said, e. g., Moore (1932) that the endocrine function of the testis is quite normal. This observation is unquestionably true in instances where the cryptorchid condition has existed for a relatively short time. Most observations on the rat have continued for only a few months and as far as the writer knows none have been made in cases of more than six months. In the guinea pig, the other animal commonly used in these studies, one year has been the maximum. In man the reports on cryptorchid testes, naturally occurring cases, of course, are uniformly lacking in precise evidence regarding the condition of the accessories.

This question first aroused the interest of the writer during

an investigation of the hormonic control exerted over the pituitary by the testis. It had been claimed by Mottram and Cramer (1923) and more recently by McCullagh (1932) that the germinal epithelium produces a hormone that has nothing to do with the stimulation of the sex-accessories, but which is concerned with the control of the hypophysis. This control, briefly, is essentially an inhibitory effect. Thus, removal of the gonad is followed by a condition of hyperactivity in the anterior pituitary. In animals whose testes are damaged by cryptorchidy, x-ray, or vitamin deficiency the hypophyses show much the same reaction as after castration. Inasmuch as the sex-accessories of such animals are normal it was reasoned that the testis-hormone which is concerned in the activation of the accessory organs does not affect the hypophysis. It followed, with this line of reasoning, that the testis produces a different hormone and, since the spermatogenic elements are damaged by the various treatments mentioned above, it seemed logical to suppose that this second hormone is produced in the seminiferous tubules. McCullagh's experiments led him to postulate that this hormone is a water-soluble substance, in contrast to the fat-soluble hormone which stimulates the sex-accessories. On the other hand, the writer had been able to show that the fat-soluble hormone does exert a controlling effect on the hypophysis (Nelson and Gallagher, 1935). It was observed, however, that the quantity of hormone required to achieve the end-point was considerably greater than the amount necessary for maintenance of the sex-accessories. These findings strongly urged the possibility that a single testis-hormone might be concerned in the control of hypophysis and sex-accessories, and suggested that perhaps a more exhaustive study of the cryptorchid animal, than had hitherto been made, should be undertaken.

Accordingly, a large group of young male rats were set aside for study. Eighty-seven of these were made cryptorchid and sixty-nine were castrated. All operations were made between the ages of 39 and 44 days. Fifty-eight males selected from the same litters as the above animals were set aside as untreated controls. Later an additional thirty-six males were made cryptorchid. No castrate or unoperated controls were included in this series.

At intervals of about 30 days representatives of three groups were sacrificed and the pituitaries, testes, seminal vesicles and prostates were removed, weighed and prepared for study. Thus

animals were sacrificed at intervals from the thirtieth to the five hundred and tenth day after operation. The number of animals sacrificed at each stage varied somewhat, but in general there were three or four cryptorchid, three castrate, and three normal animals. The occasional death of experimental animals during the long period of time covered by the experiment added cases which did not fit into the regular intervals of the experiment. Table 1 shows the data collected on the sex-accessories of the cryptorchid animals together with a part of the data for the castrate and normal animals. It will be observed that the seminal vesicles of the cryptorchid animals continued to develop normally for about six months after operation. In the animals killed after seven months the size of the seminal vesicles was was slightly decreased, but the difference is not marked. However, after 240 days there was a marked decrease in the size of the seminal vesicles, and the beginning of histological evidence for a decreased male hormone effect. During the succeeding months this became progressively more apparent until the size of the seminal vesicles was only slightly larger than that of castrates and the histological pattern was not distinguishable from the castrate. The prostate gland retained a normal size and structure until about 400 days after operation. After 500 days the size of the prostate was markedly decreased, but still considerably above the castrate level. Histologically the gland showed evidence of a lowered male hormone effect.

The fact that the seminal vesicles show "castration effects," i. e., a lowered male hormone level, in advance of the prostate is not surprising since it has been shown that the seminal vesicles require from 2 to 3 times as much male hormone as the prostates to prevent or correct the changes induced by gonadectomy. Of further interest are the observations that were made on the hypophyses of the animals in the cryptorchid series. Changes which closely simulated those occurring in the pituitaries of castrate animals, but appearing later than in the castrate controls, were present. After 75 days the "castration changes" in the pituitaries were marked enough to definitely indicate a lowered output of hormone by the cryptorchid testis. It had been shown in earlier studies that the hypophysis required about twice as much male hormones as the seminal vesicle to prevent castration changes. Thus the three organs which were used to gauge the production of male hormone by the cryptorchid testis showed castration changes in the following order: pituitary,

seminal vesicle, prostate. Furthermore, as has been noted, this order corresponds exactly with the relative requirements of these organs for male hormone. Since the hormone requirement of the pituitary is very high it is not surprising that it should be the first to show castration changes in an animal whose testis-hormone production is decreasing. It is to be expected that the seminal vesicle would show changes later than the pituitary, but in advance of the prostate whose hormone requirement is relatively low.

In addition to demonstrating for the first time that the cryptorchid testis does not maintain a normal output of male hormone this experiment seems to indicate that it is quite unnecessary to postulate the existence of a separate hormone, produced in the seminiferous tubules, which controls the anterior hypophysis. It seems reasonable to explain the hormonic control exerted by the testis over the several organs on the basis of a single hormone. In the light of our present knowledge this hormone probably is testosterone. In view of the many allied substances which qualitively resemble the activity of testosterone it would be unwise to assume that the mother substance, e. g., testosterone, circulates in the blood unchanged and provides the necessary effect upon the hypophysis and the sex-accessories. It is quite possible that the mother hormone undergoes some change before it acts upon any one or all of the end-organs. The major point to be emphasized here is the fact that the hormone active in the control of the pituitary as well as the sex-accessories is a sterol, not a water-soluble substance.

Although the testes of the long-time cryptorchid rat are not producing sufficient male hormone to maintain a normal pituitary or sex-accessories it is possible to stimulate them to do so. In a series of 25 males which had been cryptorchid for 360 to 450 days each animal was operated upon for the removal of one testis, one seminal vesicle and a piece of prostate. The condition of these tissues was the same as has been previously outlined. These animals were then injected daily with 50 rat units of Antuitrin-S (an extract of pregnancy urine containing gonad-stimulating hormone) for 10, 20, or 30 days. At the end of the experimental period the animals were sacrificed and the hypophyses, the remaining testis and seminal vesicle, and the prostate were removed for study. The results of this experiment were striking. In all animals the seminal vesicles and prostates removed after the period of treatment were histologically nor-

mal and were as large or larger than normal. In many instances the seminal vesicle removed after the period of treatment was ten times as heavy as the one removed for control purposes. The pituitaries also showed the effect of an increased output of testis-hormone. The castration changes, which in the 360–450 day cryptorchid animal are very marked, were completely corrected in the animals treated for 30 days. The testes obtained after the period of treatment were slightly heavier than the control testes. Histological study showed that this was due entirely to a slight increase in the size and number of interstitial cells. In view of the marked increase in male-hormone production it was surprising to find relatively little change in the interstitial cells.

The fact that the hormone production of the cryptorchid testis may be stimulated by gonadotropic hormone suggests that the hypophysis of the cryptorchid animal is basically at fault. This is surprising in view of the fact that it has been shown by a number of workers that hypophyses from cryptorchid animals contain more gonadotropic hormone than do hypophyses from normal males. These results were obtained with animals which had been cryptorchid for relatively short periods of time and may not apply for cases of longer duration. The results of the experiments recounted here suggest that such is probably the case and they urge the re-examination of the accepted idea that the presence of many enlarged and vacuolated basophiles is always indicative of increased gonadotropic activity of the hypophysis.

We have described the important relation between the hypophyseal gonadotropic hormones and the testis. There can be no doubt that normal testicular function is dependent, basically, upon the hypophysis. There is, however, an accumulating body of evidence which indicates that the testicular hormone itself plays some role in the production of sperm. The first suggestion of this relationship appeared in the report of Walsh, Cuyler and McCullagh (1934) that crude extracts of male hormone would not only maintain the sex-accessories of hypophysectomized males, but would also maintain the testes in an entirely normal condition. This amazing finding was finally confirmed by Nelson and Gallagher (1936) using extracts of male hormone prepared from human urine. It was shown, however, that only the spermatogenic elements of the testis were maintained in a normal condition. The atrophic changes

which occur in the interstitial cells after hypophysectomy were not prevented. At first consideration it would appear that the physiological dictum, which states that the secretion of a gland has no stimulating effect on that gland, is distinctly violated by

TABLE I

CRYPTORCHID MALES

(Figures are Averages)

No. of Animals	Experimental Period	Body Weight (gms.)	Seminal Vesicles (gms.)	Ventral Prostate (gms.)
3	30	198	.529	.279
3	64	228	.765	.374
2	73	247	1.087	.428
3	84	243	1.005	.419
4	96	259	1.102	.436
3	120	278	1.040	.460
3	148	287	.943	.402
3	182	298	.968	.437
3	210	332	.877	.422
5	240	347	.354	.398
5	273	342	.153	.377
3	300	357	.125	.394
3	330	345	.097	.349
4	360	367	.119	.327
3	394	363	.086	.293
3	421	341	.091	.174
4	450	369	.075	.117
4	482	374	.052	.122
3	510	343	.057	.109
		CASTRATE MALES		
3	30	175	.041	.052
4	96	238	.024	.042
3	240	303	.026	.037
3	300	328	.019	.033
3	510	323	.021	.035
		NORMAL MALES		
3	30	217	.576	.268
2	96	295	.737	.345
3	240	378	.1216	.478
3	300	406	.1375	.462
3	510	427	1.284	.484

the results reported above. However, this is only an apparent violation if one remembers that the male-hormone is produced by the interstitial cells and that the latter have not been stimulated by the androgenic hormone, at least in the amounts thus far employed. Table 1 summarizes the pertinent data on these

observations. It should be noted that injections of male hormone must be initiated within 12 days after hypophysectomy if spermatogenesis is to be maintained. In instances where animals were allowed to remain untreated for longer periods spermatogenesis ceased or if treatment was postponed for 3 or 4 weeks it was not possible to reinitiate spermatogenesis.

In addition to confirming the original observations of Walsh, Cuyler and McCullagh it has been possible to show that male hormone extracts will maintain normal spermatogenic activity in the testis of the hypophysectomized animal for as long as 60 days. These males have marked libido and in a number of instances have sired normal litters. This is of considerable importance since it definitely proves that the sperm which are produced after hypophysectomy are quite normal. Furthermore this observation sheds light upon the question of the control of libido in the male animal. Since libido is lost more rapidly after hypophysectomy than after castration it has been supposed that the male hormone has little to do with libido. The evidence related here renders that supposition open to question since male hormone, in the entire absence of the hypophysis, will restore libido. A more reasonable explanation for the rapid loss of libido after hypophysectomy would be based upon the more serious consequences attendant upon ablation of the pituitary.

Although the very nature of the procedure employed in preparing the extracts almost definitely eliminated the possibility that gonadotropic hormone had been present in the extracts, and consequently have been responsible for the maintenance of spermatogenesis, we made a study of the effect of the material on the immature rat ovary. Even in very large dosage no stimulating effect could be demonstrated.

The recent availability of the male hormone in crystalline form permitted a further check of the absence of a pituitary effect as contributing to the results observed with the urine concentrates. Furthermore, it was hoped that the use of crystalline androgenic substances in the hypophysectomized male would be of value in elucidating the nature of the action of the male hormone on the testis. The results with the urine concentrates had suggested that the explanation might be found in the fact that the scrotum of the hypophysectomized male injected with male hormone is maintained in a normal condition while the scrotum of the untreated control regresses. It seemed possible that this regression of the scrotum might be an impor-

tant factor in the atrophy of the testes since the latter are apparently forced into the inguinal canal and finally into the abdomen. The higher temperature of the abdomen would possibly contribute to the cessation of spermatogenesis and might be the major factor responsible for it as it is in the case of cryptorchid testes. Since the testes of animals treated with male hormone are retained in scrota which appear normal it seemed reasonable to entertain the theory that scrotal maintenance might be responsible for the continuation of spermatogenesis in the absence of the pituitary. Although this idea appeared to be a satisfactory and simple explanation for the observations on animals treated with the urine concentrates the results with the crystalline androgens do not support it.

The crystalline androgens used in this study were testosterone, androsterone, dehydroandrosterone, androstanedione, androstenediol (trans), androstenediol (cis) and androstenedione. All of them were prepared synthetically.

Testosterone is the most potent androgenic substance that has been prepared. It was first obtained from testis tissue and is supposed to be the true testicular hormone.

Androsterone occurs in urine and probably was the active substance in the urine concentrates employed in the earlier studies. It is prepared from cholesterol and has about one-tenth the androgenic activity of testosterone. Androsterone is used as the international standard for the comparison of the androgenic activity of crystalline substances.

Dehydroandrosterone is also found in human urine. It has been synthesized and has about one-half the activity of androsterone.

Androstanedione has not been found to occur naturally, but has been synthesized from androsterone. It has slightly less androgenic activity than androsterone.

Androstenediol (trans) and androstenediol (cis) do not occur naturally but are synthesized from testosterone. The former has a lower androgenic potency than dehydroandrosterone while the latter Androstenedione does not occur naturally but is prepared from dehydroandrosterone. It has about the same activity as androsterone. For a complete discussion of these and other androgenic substances the reader is referred to the recent review by Koch (1937).

In the present study of the action of these substances the routine procedure adopted for their administration was the

TABLE II

HYPOPHYSECTOMIZED MALES TREATED WITH ANDROGENIC HORMONES
(Weights are given as averages)

No. of Rats	Body Weights		Hyp. Period Days	Treatment			Organ Weights (gms.)			Sperm Motility
	First	Last		Period Days	Hormone (daily dose)	Testes	Seminal (full)	Vesicles (empty)	Prostate	
Testosterone										
3	229	195	23-24	20-21	2 mg.	1.287	2.982	.877	.733	Exc.
4	275	232	23-24	20-21	1 mg.	1.243	1.815	.651	.472	Exc.
5	243	203	23-24	20-21	0.5 mg.	1.158	1.464	.519	.463	V. good
Androsterone										
3	272	230	23-24	20-21	2.5 mg.	2.214	1.609	.529	.483	Exc.
3	281	237	23-24	20-21	1.5 mg.	1.882	1.159	.436	.365	Exc.
3	238	197	23-24	20-21	1.0 mg.	1.785	.958	.363	.277	V. good
2	226	185	23	20	0.5 mg.	1.963	.498	.355	.220	V. good
Dehydroandrosterone										
3	245	210	23-24	20-21	3.0 mg.	2.120	1.145	.443	.454	Exc.
2	242	212	23-24	20-21	2.0 mg.	2.019	.859	.335	.359	Exc.
3	239	210	23	20	1.0 mg.	1.789	.627	.295	.276	Exc.
2	242	213	24	21	0.5 mg.	1.317	.....	.163	.075	Good
Androstanedione										
5	276	219	23-24	20-21	1.5 mg.	2.379	1.529	.442	.517	Exc.
2	244	197	23-24	20-21	1.0 mg.	2.117	1.297	.375	.415	Exc.
3	248	207	23	20	0.5 mg.	2.141	.350	.206	.170	Exc.
2	237	208	23	20	0.25 mg.	1.221	.209	.175	.137	Good
1	290	247	23	20	0.125 mg.	.899	.....	.139	.073	No Mot.
Androstenedione										
2	228	177	23	20	1.0 mg.	2.016	1.241	.460	.515	Exc.
Androstenediol (cis)										
2	239	196	23	20	1.0 mg.	1.790	.497	.312	.215	Exc.
Androstenediol (trans)										
2	225	185	23	20	1.0 mg.	.750	.142	.113	.084	No Mot.
Controls										
12	278	217	22-24	.....	.....	.527	.....	.083	.054	No Sp.
Normals										
21	267	.....	.....	.....	.....	2.432	.963	.281	.295	Exc.

solution of the materials in peanut oil so that the desired daily amount was given in one-half cc. The animals used were adult male rats four or five months of age. Injections were begun on the second day after hypophysectomy and were continued for 20 days. Table 2 summarizes the pertinent data in these experiments.

It will be noted that although all of the synthetic materials with the exception of androstenediol (trans) were active in maintaining spermatogenesis, testosterone, which is the most potent of the androgenic substances is the poorest, with the exception of androstenediol (trans), in spermatogenic effect.

TABLE III

Comparison of Androgenic Substances on the Basis of the Various Tests

	Testes	Sex-Accessory Hypophysectomized Rat	Castrated Rat	Comb-Growth
Androstanedione	1	2	4	4
Androstenedione	2	3	2	3
Androstenediol (cis)	3	6	5	6
Dehydroandrosterone	4	5	6	5
Androsterone	5	4	3	2
Testosterone	6	1	1	1
Androstenediol (trans)	7	7	7	7

Androstanedione, a relatively weak androgen is the most active of the substances studied in maintaining the testis. This same lack of relationship between the potency in stimulating the sex-accessories and in maintaining spermatogenesis was shown by the other substances. Table 3 presents the rating for these compounds in terms of their capacity to maintain the testes in hypophysectomized rats and, for the sake of comparison, their potency values in the comb growth and sex-accessory tests. It is evident that the varying action of the different androgenic substances upon the testes cannot be ascribed to their potency in terms of male hormone activity. Nor is it possible to explain the different effects upon the basis of variations in the structural make-up of the substances. Androstanedione and androsterone are saturated substances while the others are unsaturated, i. e., they have a double bond in their structure. Most of the substances have a ketone and a hydroxyl group in their structural constitution although their positions may vary. There is no relation between position of these radicals and the potency of

the compounds. Perhaps the most reasonable relationship between structural constitution and potency, insofar as maintenance of the testis is concerned, is found in the fact that the two most active substances, e. g., androstanedione and androstenedione have two ketone groups. However, dehydroandrosterone and androstenedial are very active substances and they have a ketone and a hydroxyl group, and two hydroxyl groups, respectively. This same lack of correspondence between structure and testis-maintaining potency has been observed in attempts to relate structure to androgenic, i. e., comb-growth or sex-accessory stimulation, potency.

It will be recalled that spermatogenesis could not be revived in rats hypophysectomized for several weeks with the urine concentrates. A similar failure was observed when the crystalline androgens were employed.

Attention is once more called to the tentative explanation, based upon the study of animals treated with urine concentrates, for the testis-maintaining effect of male hormone. This idea was, briefly, that the well-developed scrota of the treated animals was important in enabling the testes to remain in the scrotum and consequently in maintaining spermatogenesis. While the earlier evidence distinctly favored this interpretation the more recent observations on animals treated with the crystalline androgens have caused us to abandon the idea. These results have emphasized the fact that the scrotum is definitely stimulated by androgenic hormone. Others (Hamilton, 1936, and Cutuly, McCullagh and Cutuly, (1937) have also noted this and, indeed, have advanced the idea, noted above, to explain the effect of androgens on the testis. The scrotal stimulating effect of the androgens can be shown to be proportional to the androgenic activity of the substance under test. On this basis testosterone should be, and actually is, the most effective scrotal stimulating substance. Animals injected with it, even in doses as low as 0.25 mgm. daily have very large and pendant scrota, yet their testes are not only poorly maintained, but indeed, with the lower doses they are almost as atrophic as the testes of untreated hypophysectomized animals; yet the testes of the testosterone treated animals remain in the scrotum while those of the untreated animals are abdominal or in the inguinal canal. On the other hand low doses of dehydroandrosterone or androstanedione, e. g., 0.5 mgm. daily will maintain quite satisfactory spermatogenesis yet the sex-accessories were only

slightly stimulated and the scrota, although fairly well maintained, were definitely smaller than the scrota of testosterone-injected animals whose testes were markedly atrophied.

The lack of relationship between the androgenic potency and the capacity to maintain spermatogenesis of the crystalline substances is further portrayed by the observation that extracts of the corpus luteum will maintain spermatogenesis in hypophysectomized animals. The hormone of the corpus luteum is progesterone, a substance which is closely allied structurally to the androgenic substances. It is known that unpurified extracts contain, in addition to progesterone, a substance, epi-allopregnane-ol-one, which has a relatively low androgenic activity. That this substance probably was responsible for most of the effect obtained with corpus luteum extracts is shown by the observation that crystalline progesterone had only a slight capacity to maintain spermatogenesis (2.5 mgm. of progesterone daily was about equivalent in its effect to 0.5 mgm. of testosterone). However, the point to be emphasized is that both progesterone and progestin extracts which contain epi-allopregnane-ol-one are effective in maintaining the testis, yet neither had more than a very slight effect on the sex-accessories or the scrota.

The various experiments cited above have convinced us that the influence of the male sex-hormone on the scrotum plays a relatively minor role in the continuation of spermatogenesis in hypophysectomized animals which have received treatment with androgenic or related substances. The explanation for the maintenance of spermatogenesis, therefore, remains somewhat obscure. It is quite possible, of course, that the simplest explanation possible is the true one, viz., that the spermatogenic elements are directly stimulated by the treatment. In the absence of a more likely theory this is tentatively accepted. The major difficulty attached to its acceptance is the fact that attempts to revive spermatogenesis with male sex hormone have failed. This may, of course, be accomplished with hypophyseal gonadotropic hormone.

Although no definite explanation for the phenomenon we have discussed can be offered at this time the experiments are being continued along several different lines of attack. It is hoped that some satisfactory answer to this very puzzling action of the male sex hormone upon the organ that produces it may be forthcoming from these studies.

SUMMARY

The material discussed in this paper may be summarized briefly. The normal function of the testis depends upon several factors. Among these are the hypophyseal gonadotropic hormones, normal function of the thyroid, and certain vitamines. The testis has two functions, viz., production of sperm and of at least one hormone. The endocrine activity of the testis is concerned with the stimulation of normal function in the sex-accessory structures and with the control of hypophyseal activity. As these effects may all be produced by a single hormone it is unnecessary to postulate the existence of a water-soluble hormone produced by the seminiferous tubules.

Spermatogenesis is seriously impaired by subjection of the testis to confinement in the abdomen. It has been commonly supposed that the endocrine function of the cryptorchid testis is normal. However, it was shown that, in the rat, the production of male hormone is reduced to a very low level if the reproductive organs of animals bearing cryptorchid testes for more than eight months are studied.

Although there can be little doubt that hormones produced by the anterior hypophysis are of primary importance for normal testicular function, evidence was presented which strongly urges an important relation of the testicular hormone to the spermatogenic function of the testis. Sperm production may continue for at least 60 days after hypophysectomy if the animals are treated with preparations of male sex hormone. Such males not only have functional seminiferous tubules, but will mate with normal females and have sired normal litters.

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Wit and Wisdom Mixed with Folly

Here is an irritating, exciting, amusing and instructive book. But it is a book to be read with critical faculties full awake. Here, for example, is how the author holds up a rival theory to gentle ridicule:

"Since their arms had already undergone a process of shrinkage, owing to the lack of boughs from which to suspend the body weight, the calcium deposition and growth were concentrated in the lower extremity. Hence the arms lagged and the legs grew enormously, involving the perplexed prehumans in a postural dilemma. They had their choice of progressing in a pyramidal, quadrupedal posture, with the nose barely off the ground and what ought to be the base of the trunk elevated toward the inhospitable skies, or of attempting to balance upon their hypertrophied hind legs and to wabble through life on an unstable and shifting base of support. Owing to certain difficulties with the law of gravity encountered in depressing the intaking end of the digestive tract below the outgoing, these creatures stood up, thereby exposing a vast area of vulnerable front to a hostile world. We need not accept this theory of the evolution of human posture through mineral deficiency, but the revelation of anatomical difficulties encountered cannot fail to evoke the sympathetic understanding of our anthropoid ape critics."

Now that strikes this reviewer as splendid scientific polemic. Literary skill is used to enliven a scientific argument. But Hooton uses his wit not only to make scientific theories interesting but to broadcast his prejudices in fields where he has no scientific competence. Like all wits, Hooton is a cynic but not even a cynic (if he is also a scientist) has the right to such flagrant dogmatisms as that "crime is increasing enormously." Sorting bones, even human skull bones, in the Peabody Museum does not qualify one to assert that the masses are incapable of ever understanding evolution. When he talks anatomical structure, Hooton's hereditarianism is moderate and aware of complexities; when he comes to the more intricate problem of the functions which relate to those structures, he becomes suddenly possessed of pontifical answers. The time surely has passed when any gifted amateur can dispose of the vexed problem of the relation of education to an intelligence, deemed wholly inherited, in a single deft paragraph.

Yet one can almost forgive him even this in return for his keen analysis of the race problem, his eloquent and sane eugenics, and for the many chuckles the book affords. But let the reader beware lest he find himself as this reviewer did, chuckling loudest when Hooton is wittily expressing one's own prejudices.

—H. B. English.

Apes, Men and Morons, by Ernest A. Hooton. x+307 pp. New York, G. P. Putnams, 1937. $3.00.

THE FEMALE SEX HORMONES

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I. THE OVARIAN CYCLE

In the short period of maturity preceding rupture the Graafian follicle increases rapidly in size, a process characterized by changes in the theca interna cells and by a loosening of the ovum in its enveloping granulosa. The ovum itself attains the stage of maturation. Since in most mammals this stage of follicular maturity occurs simultaneously with the pro-oestrous phase of the cycle, that is, the stage immediately prior to sexual receptivity, and since in most species the ripe follicle ruptures spontaneously with the ensuing oestrous phase, one may generalize to the extent of stating that oestrus and ovulation are essentially contemporary phenomena in animals displaying a well-defined oestrous cycle.

The ovum after its release is carried through the Fallopian tube and, in due course, arrives in the uterine cavity—the time required for this journey averaging about three days, according to Corner, "with singular unanimity regardless of species and the widely variant length of the tube." In the uterus, in the absence of impregnation, it rapidly degenerates. In the event of fertilization, which occurs in the tube or in the body cavity, the ovum, upon reaching the uterine cavity, becomes implanted in the prepared endometrial bed, the precise process of which varies according to species. Upon fertilization, we speak of the entire cycle of activity as the "reproductive cycle," in contrast to the term "sexual cycle," applied in the absence of pregnancy.

Following upon follicular rupture and extrusion of the ovum, the walls, composed in the intact stage of rows of granulosa cells, undergo a comparatively rapid change in structure; the granulosa cells, and in some species certainly, the theca interna as well, enlarge and become fat-laden, richly supplied with capillaries, forming ultimately a prominent compact body, the *corpus luteum*. In the event of impregnation, this grows large and persists functionally until nearly the end of gestation. In the absence of fertilization it persists for a variable period, according to species; in most forms at least long enough to allow the ovum, if fertilized, to become implanted.

The primary—and first known—function of the follicular apparatus is that of nourishing and discharging the ovum. A second function, the incretory one, was discovered much more recently, and is only now coming to be understood. The corpus luteum, so far as we know, is essentially incretory in function, its secretion being quite distinct from, and in certain respects perhaps antagonistic to, that of the Graafian follicle.

II. SEARCH FOR THE OVARIAN HORMONES

With the cyclic changes which occur in the ovary as a background, it now becomes necessary to anticipate somewhat, by listing the essential endocrine functions of the female gonad as these have been established. In general, these may be summarized as:

1. Control of onset of puberty; this includes development of primary and secondary sexual characters, and, to some degree perhaps, normal body growth.
2. Maintenance of the accessory organs of reproduction.
3. Preparation of accessory organs for mating. This includes as well the behaviour-pattern of the animal.
4. Preparation of the endometrium for implantation of the fertilized egg.
5. Maintenance of the endometrium for nourishment of the embryo.
6. Preparation of the genitalia for parturition.
7. Growth and preparation of the mammary glands for lactation. (Lactation, it should be noted, is not *initiated* by gonadal hormones; this specific and climactic duty is relegated to a pituitary factor).

With this list, then, of established functions, let us consider briefly the history of the arduous researches which placed these observations upon a firm experimental basis.

Our knowledge of female reproductive physiology began with the demonstration of Knauer (1896) that transplantation of ovaries in the experimental animal prevented the uterine atrophy which characteristically follows upon oophorectomy. His observation soon was confirmed and extended, particularly by Halban (1900) who, showed, in addition, that subcutaneous ovarian transplantation in the immature castrate female guinea pig resulted in attainment of normal puberty. In short, the ovarian functions include not only *maintenance* of the genital tract but its physiological *development* as well. Halban's

observations have been confirmed and amplified in numerous laboratories since that time.

On the basis of these discoveries, an internal secretion was postulated. Conceived of as a single substance, considerable speculation arose as to its source. Early attempts at testing the secretion by the injection of ovarian extracts were largely unsuccessful or, at best, unconvincing and, although this method of approach was instituted in 1900 it was not until 1912 that Adler was able to produce indications of sexual activity in spayed animals with administration of aqueous extracts.

Numerous experiments were carried out in ensuing years, but final identification of an ovarian hormone awaited the striking experiments of Allen and Doisy (1922 *et seq.*). Their work of qualitative and quantitative assay was tremendously facilitated by a test reaction which had been unavailable to earlier investigators, namely that afforded by the vaginal smear technique, by means of which the vaginal rhythm, discovered in 1917 by Stockard and Papanicolaou, could be followed. Prior to 1917, the effects of test material injections could be ascertained only by the costly and time-consuming process of sacrificing the experimental animals. Stockard and Papanicolaou, however, found that the cellular changes in the vaginal lumen, as detected by examination of vaginal lavage contents, were rhythmic in nature, the rhythm corresponding precisely to phases in the ovarian cycle. Since such changes disappeared upon castration, their reappearance upon the injection of suitable extracts could mean only that an active principle was being employed and, moreover, that its effect could be *measured*. Using fluid aspirated from sow's ovaries, Allen and Doisy soon were able to arrive as a quantitative assay, and developed the Rat Unit of the ovarian follicular hormone. The value of their work, and the stimulus it provided to research in reproductive physiology, was incalculable. An adequate method for assaying was provided, which included at the same time a method for estimating potency. This accurate and simple means of bio-assay resulted in many new and fundamental discoveries.

Then, Frank, with his collaborators, in 1925 demonstrated the same active principle in circulating and menstrual blood in the human being. Moreover, it was shown to be cyclic in quantity, the average intermenstrual peak running about one Mouse Unit per forty cubic centimeters of blood. Larger amounts were found in the blood of pregnant women. The principle, indeed,

came to be regarded as *the* "female sex hormone." Detailed chemical work was hampered severely, however, for several years by paucity of raw material. This impasse was dissipated three years later by Zondek. In connection with his epochal work on the gonadal relations of the anterior pituitary Zondek reported that urine of pregnancy contains tremendous amounts of ovarian oestrogenic hormone. This discovery proved extremely timely, in that it provided an abundant and cheap source of material, in aqueous medium and adaptable to chemical manipulation. In consequence, from 1928 onward progress has been amazingly rapid.

Chemists were quick to appreciate the practical importance of Zondek's findings, and chemical purification proved only a matter of time; only a year later Allen and Doisy and, independently, Butenandt, reported crystallization of the oestrogenic hormone, the product of which was named "theelin" by the former investigators.

Now, the discoveries of the 1920's led many to believe in a single ovarian hormone. Here was a substance which fulfilled a great many of the functions detailed above, and it seemed probable that upon proper testing it would satisfy as well the remainder of the rigid functional requirements. Doubts still persisted in some quarters, however, and this necessitates going back again some thirty-seven years to the turn of the century.

Reference has been made already to the corpus luteum. Now, this structure is present typically during pregnancy; its invariable association with the latter condition, indeed, led to many early speculations as to its possible functional significance.

Its coincidence with gestation had been noted, for example, by John Beard, in 1897, who, on purely theoretical grounds, postulated it to be essentially an "organ of pregnancy—that it served a necessary function during the course of gestation, probably in the maintenance of conditions essential to pregnancy. His reasoning was strictly of the arm-chair variety, but it is striking to reflect how closely he hit upon the truth. The German investigator, Born, (1900) speculated also, and in somewhat more detailed manner remarked upon the fact that in placental mammals, and in them only, a fully developed corpus luteum is always present and that it acquires its peak of development just when the embryo is attached to the uterus and the placenta is beginning to form. He observed also the decidual reaction on the part of the uterine mucosa, and suggested that these changes

were the result of an internal secretion of the corpus luteum—and *not* the result of stimulus provided by the ovum-mechanism as was popularly supposed at that time. In short, the corpus luteum, by virtue of an internal secretion, prepared the mucosa for reception and implantation of the fertilized egg. Born died in the midst of his speculations, and the burden of experimental proof fell to his student Fraenkel (1903).

Reasoning that if Born were correct in assuming that implantation and placentation depend upon the corpus luteum, Fraenkel came to the conclusion that, *ipso facto*, early removal of the ovaries should prevent these phenomena from occurring. Accordingly, he extirpated the ovaries or destroyed the corpora lutea in recently mated rabbits. He was able to prove the hypothesis; implantation of embryos was prevented and pregnancy met an untimely interruption.

Leo Loeb (1907) furnished additional proof, now classical, of the incretory function of the corpus luteum. Loeb showed that the endometrium of the guinea pig, sensitized by the corpus luteum hormone, develops the decidual, or maternal, growth reaction as the result of the irritating effect of the early embryo *in utero*. For example, glass beads were inserted in the uterus following upon sterile copulation, upon the day when implantation normally should have occurred. A tumour of decidual cells developed in response. Loeb's work constituted the first experimental proof that the secretion of the corpus luteum prepares the endometrium for decidual response. This work has been amply confirmed and constituted for a long time the classical test for corpus luteum extracts. On the basis of Fraenkel's and of Loeb's observations, indeed, it was long believed by many that the corpus luteum supplied *the* ovarian hormone, and that none other was concerned.

The foregoing observations led two French investigators, Bouin and Ancel in 1910 to study the uterine changes in the rabbit, prepared in such manner as to possess functional corpora lutea in the absence of pregnancy. They utilized the fact that rabbits ovulate only upon mating, and for mating employed sterile (vasectomized) males, with the result that ovulation and corpus luteum formation was obtained without the supervention of pregnancy. Under this circumstance the corpora lutea develop just as though pregnancy had ensued, and persist for an appreciable time (some two weeks in the rabbit) during which the uterus undergoes changes typical of those occurring during

gestation—in brief, a condition of *pseudo-pregnancy*. It was noted that the endometrium, the lining membrane of the uterus, underwent a characteristic proliferation, quite similar in detail to that typical of early pregnancy, and not unlike that displayed by the human endometrium late in the menstrual cycle. These proliferative changes attained a maximum in about eight days, after which retrogression set in, and the stage of rest was resumed in slightly more than three weeks. These changes never occurred in the absence of ovulation and corpus luteum formation.

The situation rested at this point until 1929, at a time when the so-called follicular hormone was attracting almost exclusive attention, when Corner, with a background of years of histological and experimental work on the physiology of reproduction, re-investigated the problem of the corpus luteum and settled the question of a possible internal secretion once and for all in a thorough-going series of experiments. To summarize these briefly, his observations may conveniently be condensed into three statements:

Ovaries were removed from rabbits 14–20 hours *post coitum*, at a time when the ova had been in the tubes 4–10 hours. In all cases there was complete failure on the part of the uterine mucosa to produce progestational changes such as those to be seen in intact females following upon mating. Embryos failed to survive. This observation confirmed Fraenkel and Ancel and Bouin.

Females were mated and, 18 hours later, were spayed, at which time small portions of the uterus were removed for examination. Injections then were given of a corpus luteum extract (obtained from the ovaries of pregnant sows). Upon the 6th day the animals were sacrificed, the embryos and uterus removed and examined histologically. In all respects both presented the same appearance as similar preparations from the intact 6-day pregnant animal.

Controls, carried out precisely as the foregoing, were given follicular hormone in place of the corpus luteum extract. As in the initial observations, none of the embryos lived, and the mucosa revealed no progestational changes.

As this very sketchy resumé shows, then, Corner's excellent work placed the proof of incretory function of the corpus luteum upon a firmly established basis. The active principle was named "progestin," and the observations made in the

Rochester laboratory soon were amply confirmed elsewhere. Corner and his student, Willard Allen, studied the various properties of their extract and continued its purification, a procedure which culminated in 1933 in the announcement of a crystalline product possessing all the known properties of the active principle. This was confirmed almost immediately in a number of laboratories (e. g. Fels and Slotta). Its structure was quickly established (Wintersteiner and Allen; Slotta *et alii*), and it was assigned the empirical formula $C_{21}H_{30}O_2$.

III. CHEMISTRY OF THE FEMALE SEX HORMONES

With the experimental proof established, and the purification achieved, let us next consider the progress attained in studies of the chemistry of these principles.

At the time the oestrogenic hormone was isolated and crystallized, Doisy gave it the empirical formula $C_{18}H_{22}O_2$ (theelin). Difficulty was anticipated, however, in clearing up its structural formula, and one would have been optimistic indeed at the time to have predicted that in the space of a few years this would be completely solved. We have here an instance, however, of how progress in a field apparently quite remote helped provide an extremely valuable key to the solution of the chemistry of gonadal principles. Fundamental researches by Windaus and Wieland culminated in 1928 by their demonstration of a close structural relationship between the bile acids and the sterols, in the course of which—and relevant to the subject at hand—they unravelled the chemistry of cholesterol. Capitalizing upon this work, Butenandt, in 1933, was able to show that structurally the sex hormones are related to this same group—a fact which had been suspected for some time. Moreover, pregnandiol $C_{21}H_{36}O_2$, a physiologically inert substance from pregnancy urine (Marrian, 1929; Butenandt 1929), separable from theelin and theelol, was converted by Butenandt into *progesterone*, the purified progestin. It is not inconceivable, furthermore, that pregnandiol, in turn might be formed in the body from cholesterol, and might be regarded as an intermediate stage in the formation of gonadal hormones from cholesterol (or bile acids). It should be noted incidentally that Ruzicka has reported conversion of cholesterol into male sex hormone.

Three oestrogenic principles have been obtained from female tissues: oestrone—$C_{18}H_{22}O_2$, oestriol—$C_{18}H_{24}O_3$, and oestradiol—$C_{18}H_{24}O_2$, the last a dihydroxy derivative of oestrone, or

dihydro-oestrone. In addition, the corpus luteum hormone, progesterone—$C_{21}H_{30}O_2$ has been isolated. Several additional oestrogenic principles have been reported, some, for example, from the urine of mares: equilin—$C_{18}H_{20}O_2$, and equilenin—$C_{18}H_{18}O_2$ (Girard, 1933).

All the sex principles possess a cyclopen taphenanthrene four-ring structure (Marrian and Haslewood, 1932) and are strikingly similar as to degree of oxidation and unsaturation.

Oestrone (theelin of Doisy) is an unsaturated hydroxyketone. Oestriol (theelol) is a trihydroxy compound, discovered by Marrian shortly after Allen and Doisy's announcement of theelin. Both these products are recoverable from urine. Butenandt and Hildebrandt demonstrated that oestriol can be converted into oestrone by dehydration *in vacuo* with potassium bisulfate.

Schwenk and Hildebrandt then reported an extremely important finding in the discovery of a dihydro derivative of oestrone —oestradiol, obtained through reduction of the ketone group to a secondary alcohol, the point of interest being that this compound is six times more potent than the oestrone from which it is derived. More striking still, this substance was soon isolated from liquor folliculi, the follicular fluid of the normal ovary by MacCorquodale *et alii* in Doisy's laboratory. There is reason to believe that it represents the pure female sex hormone, or "mother hormone," of which oestrone and oestriol are oxidation products.

Collip, in 1930 discovered an additional oestrogenic compound, recovered from urine of pregnancy. It was soon obtained in crystalline form and, regarded by Collip as a placental hormone, was given the name "emmenin," an ester of oestriol. It is of interest further to note that Andrew and Fenger have recently reported isolation of a crystalline nitrogenous compound from ovarian tissue, which is unique in that it apparently produces a delayed but prolonged oestrus in test animals, and, moreover, in that it appears to be much more powerful that oestrone. More work is needed, however, to establish clearly its separate identity.

Collip's emmenin is effective when administered orally, whereas other sex hormones are efficacious only upon injection—unless tremendous quantities are administered. Fed to immature female rats, it readily induces a condition of oestrus, without evoking any ovarian changes. It is practically ineffective in

adult rats, normal or castrate, differing sharply from the other oestrogenic compounds in this respect. Marrian and his co-workers have established emmenin as oestriol glycuronate moreover it was demonstrated that during pregnancy practically all—99%—of oestrogenic material is excreted in this form or in similar combination. Physiologically much less active than oestrone, the opinion has been advanced that the formation of oestriol, followed by the formation of its glycuronate, constitute a protective mechanism against an over-activity of oestrone and oestradiol during the course of gestation.

Finally, progesterone, an unsaturated diketone, isolated in crystalline form, as mentioned, by Allen and Corner, Fels and Slotta. Its chemical nature was established beyond further doubt by the conversion of pregnandiol (*vide supra*) and of stigmasterol, a plant sterol—specifically the wax from soy beans—into the active substance.

Is there any significance to the fact that the sex hormones appear closely related to the sterols? This seems highly probable, when we consider that the latter group of compounds are regarded as vitally important constituents of living matter. The apparent relationship is highly suggestive, although our knowledge here begin to transgress the borderline of speculation, and further work is necessary. The probable significance has been suggested by Riddle, however, in the statement that "The artificial preparation of these sex hormones from sterols suggests that *in vivo* they are intermediary metabolites or derivatives of sterols. Certain differentiated cells in the ovary (and testis as well) perhaps also placenta, apparently have the power to make these conversions. In the female, oestrone and oestriol appear to be oxidation products of the hormone actually produced by the ovary."

IV. GONADOMIMETIC ACTIVITY OF THE PLACENTA

The placenta is primarily a structure developed during pregnancy for the nourishment and respiratory exchange of the embryo. In recent years, in addition to this long-known function, sporadic evidence has appeared which has been interpreted by some investigators to indicate an actual mechanism of internal secretion. It becomes difficult, indeed, to explain certain observations on any other basis. Certainly, at least, the placenta is definitely concerned in hormonal interrelations. Without going into detail, it should be noted that Halban

(1905) pointed out that, from a clinical standpoint, the placenta must serve an endocrine function. It has since been reported that in the human being the production of ovarian hormones continues unabated following oophorectomy—the source in this circumstance having been ascribed to placental tissue (Waldstein, 1929; Probstner, 1931). Moreover, Allen and Doisy, in their search for the distribution of oestrin, found especially large quantities in the human placenta—the amount increasing progressively with the course of pregnancy. Collip, as mentioned above, has isolated a substance, emmenin, from pregnancy urine which he regards as placental in origin.

Evidence with respect to progestin elaboration by placental tissue still is uncertain. Adler, de Fremery and Tausk (1934) reported finding detectable quantities of progestin in the human placenta at term—although whether this means that it is elaborated there, or merely is retained has not been ascertained. Selye, Collip and Thomson (1935) are of the opinion that secretion of progestin occurs, since the rat uterus will show well-defined progestational changes, and the mammary glands will be maintained in a well developed condition for periods up to six days following upon ablation of the ovaries and embryos. We have obtained evidence, moreover, indicative of the role played by the placenta in maintaining hormonal balance during gestation—evidence which may be interpreted in support of the progestin-secreting concept.

It is well known, for example, that removal of the ovaries during pregnancy, at least in the more common laboratory animals, will bring gestation to an abrupt end (e. g., dog, rabbit, mouse, rat, opossum). The rule is not an invariable one, however, since it was reported some time ago that the guinea pig will frequently carry to term in the absence of ovarian tissue (Herrick; Nelson). Oophorectomy in the mare, moreover, appears to exercise no adverse effect upon the course of gestation (Cole) and, finally, the human being furnishes probably the most striking exception of all, since ablation of the gonads even in very early pregnancy may exercise no deleterious influence (Pratt; Waldstein *et al*).

In these exceptions, however, either the pregnancies are in species characteristically monotocous, i. e., in which only one fetus is carried, or the litter size is frequently limited. In the guinea pig, as an example of the latter class, the number of young ranges from one to four, and scrutiny of data reveals that

successful pregnancies after oophorectomy have been confined to animals carrying litters of not more than two. It would seem, *a priori*, that litter size may have some relation to the relative dependence upon ovarian support throughout pregnancy. When put to experimental test in the rat, this concept is borne out.

Rats commonly carry litters ranging from five to ten and twelve in number. If, however, the number of young is reduced by surgical intervention to a single fetus, removal of the ovaries shortly after midpregnancy does not interrupt the course of gestation, *provided* the additional placentae, i. e., those of the

TABLE I

EFFECT OF PLACENTAL RETENTION FOLLOWING LITTER-SIZE REDUCTION AND OOPHORECTOMY

RAT	Laparotomy*	Oophorectomy	Result
1	13†	15	23; live fetus, 5.5 gm.; 4 extra placentae.
2	14	16	23; live fetus, 5.1 gm.; 3 extra placentae.
3	13	15	22; live fetus, 4.7 gm.; 3 extra placentae.
4	12	14	24; live fetus, 5.0 gm.; not viable; 2 extra placentae.
5	13	15	23; live fetus, 4.9 gm.; 4 extra placentae.
6	13	15	23; live fetus, 5.1 gm.; not viable; 3 placentae.
7	13	15	22; live fetus, 5.0 gm.; 3 extra placentae.
8	12	14	23; live fetus, not viable; 5 extra placentae, 3 of which were detached.
9	13	16	23; fetus, 4.8 gm. alive, but died shortly after removal; 3 extra placentae.
10	13	15	23; live fetus, 4.8 gm.; 4 extra placentae, 1 detached.

*Involving removal of one ovary and fetuses in excess of one.

†The figure in each column in this and in following tables represents the day of pregnancy when operation or sacrifice was carried out.

removed fetuses, have been allowed to remain *in situ* (Table 1). As noted in the table, in ten experimental animals, in every case the remaining fetus was carried to term, and was recovered alive after being allowed to remain *in utero* for one to two days past the expected time of parturition. Spontaneous delivery does not occur—the birth mechanism, in the rat at least, appears to be seriously impaired.

The necessity for the presence of adequate placental tissue for the continuance of gestation under these circumstances is revealed by examination of Table 2, a summary of cases, operated as in the first series, in which, however, the extra placentae were included in removal. In no case was pregnancy

continued to term. Retention of one ovary under identical conditions, however (Table 3), sufficed to maintain a successful pregnancy.

TABLE II

Effect of Removal of Fetuses and Placentae, with Oophorectomy

Rat	Laparotomy	Oophorectomy	Result
15	12	15	20; placenta *in situ*, large. No fetus.
16	12	14	20; uterus empty and involuted.
17	12	15	21; uterus empty and involuted.
18	13	15	21; uterus empty and involuted.
19	12	15	21; uterus empty and involuted.
20	14	16	20; term-sized placenta *in situ;* no fetus.
21	13	15	20; uterus empty and involuting.
22	12	15	21; uterus empty and involuted.
23	13	15	22; uterus empty and involuted.
24	12	16	Allowed to run to 24th day. No evidence of delivery. Atrophic uterus upon post-mortem.
25	13	15	22; one small placenta, unattached.

It would appear therefore that presence of the ovaries is not necessarily essential during the entire course of gestation, even in the polytocous rat, provided too many young are not being carried and provided further that adequate viable placental

TABLE III

Effect of Retention of One Ovary Following Removal of Excess Fetuses and Placentae

Rat	Laparotomy	Result
31	12	Delivered one fetus 22nd day; perfectly normal.
32	12	Delivered one fetus 21st day; killed by mother.
33	13	Delivered one fetus 22nd day; fetus died following day.
34	14	Delivered one fetus 22nd day; perfectly normal.
35	15	Delivered one fetus 21st day; perfectly normal.
36	14	Delivered one dead fetus 21st day.
37	14	No delivery. Empty uterus at 23rd day autopsy.
38	14	Delivered one fetus 22nd day; perfectly normal.
41	13	Delivered one fetus 22nd day; perfectly normal.
42	15	Delivered one fetus 22nd day; killed by mother.

tissue is present. The question of paramount importance is that of how the placental tissue functions in maintaining pregnancy. We do not know the answer to that as yet, since there is no evidence available that the rat placenta actually secretes pro-

gestin. The working hypothesis has been advanced that a progestin-secreting mechanism most satisfactorily explains the observations noted, but this is as yet only a hypothesis. In all events it is quite evident that the placenta serves as an adjunct to the ovaries as an endocrine mechanism—or is concerned in maintaining a proper endocrine balance. Its capacity in this respect is in all probability better developed in some species than in others—in the mare or the human being, for example, in which the corpus luteum regresses or becomes non-functional at a relatively early age and in which, presumably, the placenta can assume the functional attributes of ovarian tissue in regulating endocrine balance.

The concept of the placenta as an auxiliary gland, capable of secreting progestin, or a progestin-like principle, during pregnancy would serve to explain the curious fact that oophorectomy in some forms need not terminate pregnancy, and at the same time would not be at variance with our concept concerning the importance of the luteal hormone during pregnancy. Further work is indicated, however, before we can speak with certainty.

In conclusion, an attempt has been made in this very brief sketch to indicate the major functions of the female sex hormones. A brief survey of their discovery has been sketched, including the highlights of the final triumph of their purification, chemical elucidation and synthesis. Evidence pointing to the placenta as a possible auxiliary organ of internal secretion has been touched upon, and, although conclusive evidence awaits further experimentation, the role of the placenta in maintaining hormonal balance is such as to justify, in the writer's opinion, use of the term "gonadomimetic" with reference to its endocrine activities.

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Radiant Energy

During the first thirty-five years following its birth, any branch of physical science can be expected to pass through a period of active development in which a confusion of ideas and notation comes into existence. So it has been with the measurement of radiation. This division of physical science was, for all practical purposes, born with the announcement of the Planck Radiation Law in 1900. Since that time, many methods of measuring radiation have been developed, not the least of which are the uses of the photographic emulsion and photoelectric cell. Until now, however, there has appeared no good critical survey of the field of radiation measurement. There has been much confusion and misunderstanding sometimes of simple ideas. The present volume removes this confusion and makes clear the problems to be encountered by one who would measure radiation. Under the meticulously careful editorship (and partial authorship) of W. E. Forsythe, this book, in the opinion of the reviewer, is the best of the multiauthored scientific books which have recently appeared. Its discussions are short, direct and authoritative, yet there is no loss in coherence from article to article, so carefully has the material been edited.

This book should be of great assistance to all who have occasion to measure the strength of radiant energy during the course of their work.—C. E. Hesthal.

Measurement of Radiant Energy, edited by W. E. Forsythe. xiv+452 pp. New York, the McGraw-Hill Book Co., 1937. $5.00.

Dendrology

With the new interest in forestry and soil conservation the teaching of Dendrology must be decidedly increased in our colleges and universities if properly trained men are to be available to carry on the enlarged program. Suitable textbooks are a primary necessity in this program. The present textbook includes all the important forest trees of the United States and Canada and will, no doubt, take an important place, both in the classroom and in general reading courses. It is beautifully printed and illustrated. There is a general introduction with illustrations and definitions of flower, inflorescence, fruit, leaf, and twig characters, and in the body of the text very complete general descriptions and notes, distinguishing characters, botanical features, and range of each species.

—John H. Schaffner.

Textbook of Dendrology, Covering the Important Forest Trees of the United States and Canada, by William M. Harlow and Ellwood S. Harrar. 527 pp. New York, McGraw-Hill Book Company, 1937. $4.50.

THE THYROID HORMONE

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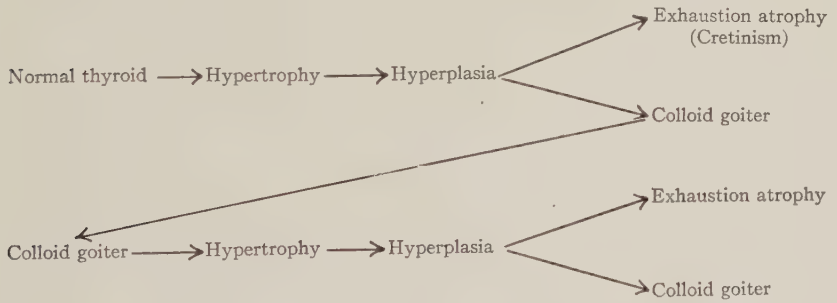
In this lecture I shall attempt to review briefly the principal facts of thyroid chemistry and physiology and some of its interrelations with other glands of internal secretion.

ANATOMY

Brief mention of the main anatomical changes will be helpful in correlating the chemical and physiological discussions which follow. *Ancestrally*, the thyroid is limited to the Chordates. In the lowest forms—tunicates, amphioxus and ammocoetes—it is represented by the endostyle organ, an elaborate midline pharyngeal epithelial groove. The connection between the endostyle organ and the ductless thyroid of all higher Chordates is established by the fortunate preservation of a single species—the lamprey—which in its larval state has an endostyle organ and in its adult form, the characteristic ductless thyroid follicles. This follicle is the thyroid unit and exists in essentially the same form in all vetebrates from the lamprey to man. It, therefore, seems safe to assume that it has essentially the same function throughout the vertebrates.

The thyroid unit is a closed rounded cyst-like vesicle of variable size (in man .05 to 0.5 mm.), lined with a single layer of low cuboidal epithelium. These epithelial cells are of two types, as first recognized by Langendorff—(1) chief cells and (2) colloid cells—and the necessary intermediate stages. These two types of cell occur in varying proportions but the chief cells in the normal gland always predominate. Because of the varying proportions of these two types of cell it is believed that they represent different stages in the secretory activity of a single cell type. The chief cell is the actively secreting cell and the colloid cell is the collapsed, spent cell. Filling the follicular spaces normally is a homogeneous amber colored globulin—the so-called colloid which gives to the thyroid its most characteristic anatomical feature. This colloid varies in density in different glands and in different follicles of the same gland and can be increased or decreased under experimentally controlled conditions which indicate that the colloid is a storage product. The

blood supply of the follicle is composed of a rich network of wide, short capillaries, very similar to that of the lung alveolus. The blood supply to the gland, as a whole, is subject to extreme variations, but even normally it ranks with the 5 or 6 most vascular organs. The thyroid is richly supplied with nerve fibers which end both in the vessel walls and around some of the gland cells. Vasomotor fibers are present in great abundance but the presence of so-called secretory or regulatory nerves is still in doubt. The fact that nerve fibers terminate in end brushes about the gland cells is evidence that they have some function, but it has been clearly demonstrated that nerve fibers are not necessary for gland function, since autotransplanted thyroid in widely separated parts of the body undergoes hyperplasia and involution simultaneously with the non-transplanted tissue and can store and excrete iodine. These manifestations of function of transplants—long known to be due to some factor reaching the cells by way of the blood stream—have in recent years been proven to be due to the thyrotropic factor of the anterior pituitary. The thyroid gland is one of the most labile tissues in the body, capable of exhibiting morphological changes within a few hours. Because of this wide range of anatomical changes we are provided with a very delicate anatomical measure of functional variations. Unfortunately attempts to interpret these changes in relation to disease have caused as much confusion as clarification. This range of morphological changes may be designated as the anatomical cycle and represented schematically as follows:



The actively hypertrophic and hyperplastic stage always indicates stimulation of the gland cells, and so far as known, this is brought about solely by the thyrotropic hormone of the anterior pituitary. The colloid stage represents the return of the hyperplastic stage to its normal or quiescent condition, and the

atrophic stage the permanently exhausted thyroid. There is no basis for assuming that the series of changes observed in the thyroid in association with simple goiter, with exophthalmic goiter, with compensatory hypertrophy following partial thyroidectomy and following the administration of anterior pituitary extracts are not essentially identical.

PHYSIOLOGY

Prior to the publication of Gull's observations (1874), "On a cretinoid state supervening in adult life in women," the function of the thyroid was either speculative—that its secretion moistened the larynx, that it served to round out the neck, that it acted as a vascular shunt for the cerebral circulation, that it aided in the formation of erythrocytes, that it neutralized toxins—or was confused with the functions of the parathyroids. Gull definitely associated atrophy of the thyroid with dryness and loss of hair, thickness and dryness of the skin and a striking deterioration of mental and physical vigor. William Ord (1878) designated this condition myxedema, because he thought the brawny thickening of the subcutaneous tissues was due to excess mucin formation. In 1882 the Reverdin brothers, and in 1883 Theodore Kocher reported more fully on the effects of total thyroidectomy in man for the cure of goiter. Their observations established the first experimental confirmation of Gull's clinical pathological observations. Kocher designated the symptom-complex *cachexia strumipriva* and recognized that it was similar to Gull's spontaneous myxedema. Following these reports many species of animals were subjected to thyroidectomy. Thyroidectomized dogs (Schiff) and cats (Smith) usually developed an acute symptom-complex (tetany) and died within a week, while rabbits, sheep and goats lived indefinitely with little or no obvious effects. No real separation of the functions of the thyroid and parathyroid was possible until E. Gley (1891), physiologically speaking, discovered the external parathyroids in the rabbit and demonstrated that the acute symptoms and fatal outcome which earlier workers had noted in man and animals following thyroidectomy was due to the removal of the parathyroids. Nearly 20 years elapsed before separate functions for the parathyroids and thyroid glands were accepted by all workers. The recent work of Aub and his coworkers indicates that there is an important interrelation between the thyroid and parathyroid as regards calcium and phosphorus metabolism.

Since 1891 many species of mammals have been subjected to thyroidectomy in which the parathyroid factor has been excluded and the results are essentially identical in all species.

The next important contribution to thyroid physiology was in 1891 when Murray cured a case of Gull's disease by a series of injections of glycerol emulsion of fresh sheep's thyroid. This was an advanced case of 5 years' duration when treatment was begun. The patient died in 1919 at the age of 74, health having been maintained for 28 years. In 1892 Howitz, Mackenzie and Fox independently demonstrated that thyroid was equally effective in curing Gull's disease when administered orally either fresh, dried or cooked.

In 1895 Magnus-Levy, using the newly developed calorimeter, discovered that in Gull's disease the heat production was lowered as much as 40 per cent. Later work showed that this lowering of metabolism (O_2 consumption, CO_2, nonprotein nitrogen output and heat production) was the characteristic effect of thyroidectomy in all animals tested. The fall in metabolism begins in most animals between the fifth and seventh day after thyroidectomy and reaches its lowest level (30–40 per cent) in the rabbit between the 20th and 30th day and in man about the 60th day. This low level of metabolism may be maintained for years or as accessory thyroids or fragments regenerate the metabolism may rise, but usually not to the normal level.

In 1895 Magnus-Levy further showed that the oral administration of thyroid substance both to cases of Gull's disease and to normal persons caused a rise in metabolism. This observation determined the principal function of the thyroid as we understand it today, namely, that it provides a means for maintaining a higher rate of metabolism and for varying the rate to meet changing physiological needs. In 1912 Gudernatsch discovered that feeding thyroid to tadpoles caused metamorphosis to occur in from 3 to 5 days. This is still the most delicate test for the thyroid hormone. It was suggested that this effect might be due to raising the metabolism but work in recent years, particularly with the dinitrophenols, shows that these substances greatly increase the metabolism of tadpoles and cases of myxedema. This increased metabolism does not cause metamorphosis of tadpoles nor does it benefit cases of Gull's disease. The thyroid hormone, therefore, has a specific action not exhibited by iodides or by metabolism raising substances (adrenalin, dinitrophenol).

Chronologically the next important contribution to thyroid physiology was the demonstration by P. E. Smith (1916) and B. M. Allen (1917) that removal of the pituitary in tadpoles caused marked involution of the thyroid. Smith later devised the pharyngeal route for hypophysectomy in the rat and established that a hormonal factor from the anterior pituitary controlled the functional state of the thyroid.

Baumann and Hunt (1925) demonstrated that the thyroid hormone is necessary for Rubner's specific dynamic action of ingested foods. In thyroidectomized rabbits it disappears completely after 60 to 65 days, but can be restored in such rabbits by the administration of desiccated thyroid or thyroxine. While qualitatively the symptoms following thyroidectomy are similar in both immature and mature animals, the visible manifestations are much more striking in the immature animal. Superficially adult rabbits, sheep and goats may show very little change, which led the earlier workers to the conclusion that thyroidectomy was without much effect. Metabolism studies, however, showed the usual marked reduction in oxidation processes. In the young, this lowering of metabolism leads to stunting physical, mental and sexual development (cretinism).

The long life of thyroidectomized animals, the fact that animals below the lampreys do not have thyroids supports the conclusion that the gland is not essential for vegetative life.

The mode of action of thyroxine in increasing oxidation processes is unknown. The stimulation is a very general one since it increases the oxidation of proteins, fats and carbohydrates in their normal proportions as indicated by the respiratory quotient. Rohrer first showed that the oxygen consumption of minced liver, kidney and muscle of rats previously fed with desiccated thyroid was increased and Ahlgren showed that muscle from thyroidectomized animals consumed less oxygen than normal muscle. Most observations indicate that thyroxine added to excised tissue in vitro is without effect. The observation of Davis, de Costa and Hastings (1934) suggests that thyroxine increases the metabolism of the excised intact frog's heart but not of slices of the heart muscle. Verebely found that thyroxine was without effect on liver and muscle cells but raised the O_2 consumption of brain tissue and came to the conclusion that thyroxine probably exerts its action on the various somatic tissues by way of the central nervous system. Cannon and his coworkers found thyroxine effective in sympathectomized cats.

This conclusion is also supported by the observation of many workers including Abderhalden and Wertheimer, H. H. Meyer, Mansfield and Issekutz. Thyroxine does not raise the metabolism of frogs and reptiles. Issekutz found that thyroxine had no effect on the basal metabolism of spinal cats and assumed, as others had, that an intact central heat regulating mechanism was necessary for thyroxine action. This conception of thyroxine action would go far toward explaining its action on general metabolism, the long latent period, the relation of thyroxine to exophthalmos production, the purpose of a relatively high iodine content of the diencephalon and its possible correlation with adrenalin, that is, adrenalin acts through a peripheral sympathetic mechanism, while thyroxine may act through the vegetative centers in the hypothalmic region.

Diet. Diet influences the thyroid. Baumann and his coworkers (1896) first noted that feeding meat diets to dogs caused a decrease in the iodine store, while feeding sea fish (high in iodine) caused an increase in the iodine store of the thyroid. Watson showed that meat diets caused thyroid hypertrophy in rats. Marine and Lenhart found that liver, especially pig's liver, was the most potent of a large variety of meats in causing thyroid hypertrophy in dogs and also that this food was an important factor in the causation of goiter in brook trout. McCarrison, and later Mellanby, showed that fats also promote thyroid hypertrophy. All these studies indicate that protein and fats increase the rate of discharge of thyroxine and therefore thyroid activity is more necessary in their oxidation than in the oxidation of carbohydrates. This conclusion was also indicated by the rise in the respiratory quotient which normally follows thyroidectomy. Rachitogenic diets, whether of the high calcium and low phosphorus or high phosphorus and low calcium type, cause thyroid enlargement in dogs, rabbits and rats, providing the iodine intake is low. This action is independent of the protein, fat and carbohydrate in the diet. Such studies indicate that the ratios of calcium, magnesium and phosphorus in some important way influence thyroid function. Thompson has shown that calcium is increasingly effective in causing thyroid hyperplasia in rats the lower the iodine intake and she has recently demonstrated that a high calcium intake requires a much higher iodine intake in order to maintain a given level of the blood iodine.

BIOCHEMISTRY

Since Coindet (1820) first demonstrated the therapeutic value of iodine in the treatment of goiter many attempts to demonstrate this element in the thyroid have been made. Coindet's observation also made it possible quickly to establish that iodine was the active agent in the remedies (burnt sponge, salt, seaweed) that had been beneficially used for centuries in the treatment of goiter. The discovery by Murray (1891) of the curative effects of thyroid opotherapy in myxedema and the demonstration a year later that the active principle withstood drying and heating stimulated biochemists to attempt to isolate it. These efforts resulted in Baumann's announcement in 1895 that iodine in stable organic combination was a normal constituent of the thyroid. He obtained a brownish powder by prolonged hydrolysis with 10 per cent sulphuric acid which contained up to 10 per cent of iodine and named it *iodothyrin*, later *thyroidin*. Subsequent work showed that this method of hydrolysis destroyed part of the specific iodine compound. For some years following Baumann's discovery there was much discussion of the question whether iodine played an essential role in the active substance. Hutchinson (1896) concluded that the iodine containing colloid matter was the active substance: "The part which the iodine plays it plays in virtue of the form of combination in which it occurs in the colloid, not in virtue of its being iodine." Magnus-Levy (1897) had clearly demonstrated that iodides did not increase metabolism. Baumann and his pupils showed that iodine was present in dogs' thyroids in variable amounts and that feeding iodine increased the store, while feeding meat decreased the store. Baumann (1897) demonstrated that human thyroid glands from Hamburg contained larger amounts of iodine than glands obtained in Freiburg. Oswald (1897) demonstrated that the iodine content in general varied directly with the amount of colloid. Oswald (1899) also confirmed and extended Hutchinson's observation that the colloid was a globulin and contained practically all of the iodine. He recognized that this globulin could be rich or poor in iodine and introduced the terms "thyroglobulin" and "iodothyroglobulin." Marine and Williams (1908) and Marine and Lenhart (1909) showed that histologically the amount of colloid material in the follicle varied inversely with the degree of epithelial hypertrophy and also that the iodine content of the

thyroid varied inversely with the degree of hyperplasia. The globulin content of the thyroid is roughly the same whether the gland is hyperplastic or colloid. In the actively hyperplastic gland the thyroglobulin is in the cells and is very poor in iodine, whereas in the normal or colloid gland (goiter) the thyroglobulin is mainly in the follicles and is usually, though not always, rich in iodine. The maximum store of the iodine in the mammalian thyroid is between 5 and 6 mg. per gram of dried gland, while the minimum may be inestimable traces. The minimum concentration necessary for the maintenance of normal structure appears to be strikingly constant in the domesticated mammals and averages around one tenth of 1 per cent dry weight. The relation of the iodine store to the histological structure of a few typical mammals is given in the following table, expressed in milligrams per gram of dried gland.

	Normal Stage	Hyperplastic Stage			Colloid or Resting Stage
		Early	Moderate	Marked	
Man	2.17	0.88	0.71	0.32	2.00
Dog	3.32	0.62	0.37	0.11	1.99
Sheep	2.47	....	0.40	0.01	3.00
Ox	3.46	1.65	....	0.19	....
Pig	2.51	1.10	....	....	2.35

The normal human thyroid weighs between 20 and 25 gm. and may contain as a maximum 1 mg. of iodine per gram of fresh tissue, while the average is about one half this amount. Iodine appears early in the fetal thyroid. Fenger demonstrated it in the fetal calf as early as the third month. There is also a definite seasonal variation in the iodine store (Seidell and Fenger), the store being lowest in early spring and highest in the late summer in cattle, sheep and pigs. Iodine fed to pregnant animals is quickly stored, both in the maternal and fetal thyroids and a depletion of iodine in the mother also reduces it in the fetus. Surviving thyroid in vitro has the same marked selective ability to take out and fix iodine (given as KI) from the circulating fluid as is seen in the thyroid in vivo. No other tissue has this capacity. So far as is known the thyroid is the only organ capable of elaborating the iodine containing hormone. Iodine is normally present in the blood. The normal amounts

reported vary widely from 8 to 18 micrograms per 100 cc. The variations reported are probably due more to the methods used, none of which are satisfactory, than to the actual variations, and probably 5 to 10 gamma per cent would more nearly represent the normal variations. In general the blood iodine has been found higher than normal in most cases of Graves' disease, but not in all cases and it is below normal in myxedema and after thyroidectomy (Curtis et al). Also in endemic goiter districts the blood iodine is generally lower than that of non-goiter districts. The presence of iodine in the blood implies that iodine should be present in minute amounts in all tissues as originally claimed by Justus and now generally confirmed. However, certain tissues have much higher iodine values than others, though none has quantities remotely approaching that of the thyroid which normally contains probably one fifth of the body iodine. The ovaries, anterior pituitary and diencephalon contain more iodine than other organs. The form in which the iodine exists in the blood and tissues other than the thyroid is not known. It is interesting but unprofitable at present to speculate on the possible physiological importance of the concentration of iodine in the diencephalon, ovaries and pituitary, particularly in relation to the known interrelations of these organs.

Iodine balance. Attempts have been made to determine the minimum daily needs of iodine in the normal human subject by iodine balance studies, particularly by Von Fellenberg, Scheffer, and Curtis and his coworkers. Such studies entail great difficulties because of the small amounts of iodine involved and the methods available of estimating its excretion in the urine, feces, sweat, respired air and nasal secretions. The daily requirements for thyroxine iodine can be more accurately determined by the amount of thyroxine necessary to hold the basal metabolism of cases of myxedema to the normal level. This has been determined by Boothby and other workers at 160–200 gamma I_2 (approximately 0.31 mg. thyroxine). A large part of this thyroxine in normal persons is undoubtedly derived from the conservation of iodine in the body. Hence it would be desirable to know how much iodine is required to balance that lost daily through the excreta in normal persons—so-called iodine balance. Studies along these lines have given figures of 15–25 gamma per day as the minimum intake necessary to balance excretion (v. Fellenberg, Scheffer, Curtis et al). The figures have been

obtained by determining over a period of some weeks the amount retained from a given daily intake and from the amounts excreted daily when the intake is reduced to as nearly nil as possible. The idea that there could be any constancy in the excretion of iodine under ordinary conditions seems so improbable to me that the physiological value of the data reported is problematical.

Returning to the attempts to isolate the active principle of the thyroid, all efforts to utilize the method of acid hydrolysis failed. Oswald tried barium hydroxide hydrolysis because Drechsel (1896) had used this method successfully in isolating iodogorgin from the axial skeleton of coral. Wheeler and Jamieson (1905) showed iodogorgin 3.5.3^1.5^1. was diiodotyrosine. Oswald failed to obtain an active fraction because, as pointed out later by Harington, he discarded the acid insoluble portion with the barium sulphate. Hutchinson, Oswald and others, also were unsuccessful, in concentrating the active principle by means of peptic and tryptic digestion. Kendall (1913) again undertook to use the method of alkaline hydrolysis and showed that the iodine became increasingly dialyzable through celloidin membranes by carefully treating thyroid with sodium hydroxide. In 1914 Kendall, by hydrolyzing thyroid with 1 per cent sodium hydroxide in 90 per cent alcohol, was able to separate the iodine of the thyroid into two fractions which he designated A and B. Fraction A, or the acid insoluble, was physiologically active, while fraction B, or the acid soluble portion, was physiologically inactive. In 1916 Kendall announced the isolation from fraction A of a crystalline compound containing approximately 65 per cent of iodine and which physiologically produced the same effects as desiccated thyroid. The yields were exceedingly poor and his attempts to determine the structure from amounts available were unsuccessful but he thought it was a derivative of tryptophane. Nurnberg (1907) using Baumann's iodothyrin attempted to ascertain the iodine holding group of thyroglobulin. He was unsuccessful but certain reactions led him to suggest that the iodine was bound with tyrosine—probably as diiodotyrosine. In 1926 Harington improved the method of extracting thyroxine by returning to the use of barium hydroxide and was able to accumulate sufficient quantities to determine its empirical formula as $C_{15}H_{11}O_4NI_4$ and its structural formula as 3.5.3^1.5^1. tetraido–4–(4^1-hydroxyphenoxy) phenyl α aminoproprionic acid. The organic nucleus he named thyronine.

Later work by Harington and Randall showed that thyronine was formed from two molecules of tyrosine with the loss of one molecule of a aminoproprionic acid and the two benzene rings joined by an ether linkage. In 1927 Harington and Barger synthesized thyroxine and showed that it had the same physiological action as natural thyroxine. Harington further showed that the acid soluble fraction, or the physiologically inactive iodine, earlier designated product B by Kendall, was diiodotyrosine and identical with that present in coral and sponge. Foster (1929) confirmed the occurrence of diiodotyrosine in the thyroid and was able to recover as much as 30 per cent of the total thyroid iodine as diiodotyrosine. It is of paleochemical interest that diiodotyrosine in protein combination is found in sponge and coral and may be the hormonal equivalent of thyroxine in these animals. Harington has estimated that diiodotyrosine on the average accounts for about 60 per cent of the thyroid iodine and thyroxine for 40 per cent. The proportion of these two compounds must obviously vary since diiodotyrosine is a stage in the synthesis of thyroxine and both substances are constituent amino acids of a specific globulin. These are the only two forms in which iodine has been found in the thyroid.

It is of interest to note that one may immunize an animal (rabbit) against ox iodothyroglobulin without affecting the physiological action of the hormone (Rosen and Marine) while with other hormones of a protein nature, such as parathormone, the anterior pituitary hormones and prolan appear to be, immunity eliminates their physiological activity. This shows that thyroxine is not an essential factor in the antigenic property of thyroglobulin while with the other hormones mentioned their antigenic properties are intimately connected with the physiologically active component of the protein. The synthesis of thyroxine by the thyroid requires hours while the storage of iodine in the surviving gland, both in vivo and vitro, is almost instantaneous. The form in which iodine is so quickly stored has not been determined but the work of Harington suggests that it may be bound with tyrosin. It is, however, firmly fixed so that prolonged perfusion will not wash it out if the cells are surviving. This is not true of other tissues. The first evidence of thyroxine formation in dogs' thyroid using the Gudernatsch tadpole test was obtained by Marine and Rogoff in about 8 hours after the intravenous injection of potassium iodide. It

has been known since thyroxine was first available that when orally administered it is much less active than an equivalent amount of iodine in the form of desiccated thyroid or of iodothyroglobulin. This has been explained as due to its insolubility and hence its poor absorption. But Reed Hunt (1923) showed that when thyroxine was injected intravenously and iodine equivalent amounts of desiccated thyroid administered orally thyroxine was less active, thus establishing that the total iodine of thyroglobulin (thyroxine and diiodotyrosine) was physiologically active. Recently this fact has been confirmed in another way. Rihl, Oestreicher and Reiss (1936) showed that in the rabbit the pulse rate rises almost immediately after the injection of thyrotropic hormone, whereas when thyroxine is injected no effect on pulse rate is noted for more than 6 hours.

Salter and Lerner have suggested that diiodotyrosine is a cohormone and the thyroid hormone is complete only when diiodotyrosine and thyroxine are combined in the peptone molecule. In support of their hypothesis they have taken the relatively inactive (as tested on cases of myxedema) diiodotyrosine peptone residue from human thyroglobulin after removing most of the thyroxine and with the aid of pepsin have resynthesized a protein that was as effective in relieving myxedema as natural thyroglobulin in iodine equivalent doses. No explanation of what has happened under these conditions is available and the phenomenon is at present limited to the degradation products of thyroglobulin. Recently Ludwig and von Mutzenbecher have produced a substance chemically and physiologically nearly identical with thyroxine from a "non-specific protein" and iodine by hydrolyzing with weak alkali and heat. Heretofore only diiodotyrosine has been obtained by hydrolyzing non-specific protein plus iodine. Diiodotyrosine has only the action of iodides. It does not enhance the activity of thyroxine. Harington has combined the two amino acids into thyroxyl-diiodotyrosine and diiodotyrosyl-thyroxine without influencing the activity of contained thyroxine.

As the matter stands at present there is no need of assuming the existence in the thyroid of any active compounds other than those determined by iodine and thyronine. The combinations of iodine and thyronine are not the active principles but rather they are the components that confer specific properties upon a more or less complex protein fragment. This opinion is supported by the work of Harington and of Salter and his coworkers

who have found thyroxine peptone more active than glycyl or allanyl thyroxine and these in turn somewhat more active than thyroxine in experiments where all three groups of substances were given intravenously. Much work obviously remains to be done to determine why thyroxine and diiodotyrosine combined in thyroglobulin is so much more active physiologically than the equivalent amount of crystalline thyroxine and diiodotyrosine.

INTERRELATIONS

This is probably the most important and certainly the most difficult problem in the thyroid physiology and pathology.

Thyroid-Gonads. This is the oldest known interrelationship of the thyroid. It is evidenced by the frequency of enlargement of the gland during menstruation, pregnancy, puberty and the menopause. As has already been mentioned, the ovary (but not testis) is relatively high in iodine, but the form in which it occurs and its possible function are wholly unknown. Removal of the gonads in the rabbit, dog, and rat usually leads to a slow involution of the thyroid, becoming manifest in about one month and associated with a slight reduction in total metabolism. In the guinea pig, on the other hand, gonadectomy causes a definite slight temporary activation and enlargement of the thyroid. Schockaert noted that emulsions of fresh ox anterior pituitary caused greater hypertrophy of the accessory male sex glands after thyroidectomy than before. I have pointed out that thyroidectomy in puberal rabbits hastens sexual maturation and greatly increases sexual activity in the males. Both of these types of reaction are apparently mediated through the anterior pituitary, as is further indicated by the fact that administration of oestrogenic substances or aqueous extracts of the male germinal epithelium prevent the thyroid enlargement in castrated guinea pigs, while desiccated thyroid prevents increased sexual activity of thyroidectomized male rabbits.

Thyroid-Thymus. Gudernatsch (1914) observed that thymus feeding increased the rate of growth of tadpoles, definitely retarded their metamorphosis and offered some protection to them against thyroid feeding. Hoskins obtained increase in the weight of the fetal thymus in guinea pigs whose mothers had been fed desiccated thyroid. Thyroidectomy definitely hastens thymus involution. Removal of the pituitary in dogs (Houssay) usually causes involution of the thymus. In diseases in which

the thyroid activity is increased, as in exophthalmic goiter and acromegaly, thymus hypertrophy frequently occurs. All these effects could be interpreted as indicating some kind of an antagonism between thymus and thyroid hormones directly, or that they were mediated through the pituitary.

Thyroid-Parathyroids. The view that the parathyroids could function vicariously for the thyroid ended with Gley's demonstration that the so-called acute effects of thyroidectomy were due to the accompanying parathyroidectomy. The strikingly different symptoms of thyroidectomy and parathyroidectomy appeared to establish independent functions for these glands, but during the last decade evidence has accumulated indicating that they are at least complimentary in certain of their functions. The work on experimental rickets and particularly the work of Aub and his coworkers on exophthalmic goiter, thyroid feeding and myxedema shows that the thyroid is also concerned with the metabolism of calcium and phosphorus. The idea that excessive calcium ingestion was a causal factor in goiter was suggested a century ago (McClellan 1837). Aub has shown that in Graves' disease the calcium excretion is greatly increased while in myxedema it is lessened. Both thyroid feeding and the administration of the thyrotropic hormone greatly increase calcium excretion (Pugsley). Excessive thyroid feeding causes parathyroid hypertrophy. The increased thyroid activity in animals (dogs, rats, rabbits) on rachitogenic diets is associated with parathyroid hypertrophy. Thyroidectomy in rabbits on diets with normal Ca:P shows involution of the parathyroids. Baumann (unpublished) has shown that thyroidectomized rabbits on a high phosphorus and low calcium diet die more quickly than normals—suggesting that the thyroid enlargement on rachitogenic diets is protective in nature.

Thyroid-Chromaffin System. Some interrelation is indicated because of the facts that thyroxine and epinephrine are both derivatives of tyrosin and that both are powerful activators of metabolism through different mechanisms. Also as Goldberg and others have noted in thyroidectomized lambs—and we have confirmed in thyroidectomized rabbits—the adrenal medulla is definitely hypertrophic.

Asher and Flack (1911) showed that the blood pressure response in rabbits to a given dose of adrenalin was greater after stimulation of the thyroid nerve with intact thyroid than before. This has been confirmed, particularly by Cannon and his

coworkers. Oswald has shown that a similar increase in the blood pressure response to adrenalin may be obtained by the intravenous injection of iodothyroglobulin and that the effect produced is proportional to the iodine content of the thyroglobulin injection. The Goetsch epinephrine test on exophthalmic goiter may be a clinical application of increased sensitivity to epinephrine. All these observations would support the original view of Asher and Flack that the thyroid hormone increases the irritability of the sympathetic nervous system and sensitizes the tissues innervated by it so that they are more susceptible to stimulation by epinephrine.

Thyroid-Pituitary. It has been known for nearly a century that individuals and animals with simple goiter have greatly enlarged anterior pituitaries. Niepce observed pituitaries in goitrous cretins weighing 2.4 gm. Rogowitsch (1889) was the first to produce experimentally hypertrophy of the anterior pituitary by removal of the thyroid in rabbits. This has been generally confirmed and a generalization may be made that in all states of thyroid insufficiency the anterior pituitary tends to undergo hypertrophy. Histologically all the elements of the anterior pituitary appear to take part in this hypertrophy, but the most striking single feature in rabbits is the degranulation of the acidophilic cells. The physiological significance of this thyroid-pituitary relationship became evident only after Allen and Smith devised methods for removing the pituitary in tadpoles and later by Smith developing a similar method for rats. Smith noted in tadpoles and in rats that hypophysectomy caused a marked reduction in the volume of the thyroid gland and that implants or injections of extracts of fresh anterior pituitary restored such atrophic thyroids to normal and even produced hypertrophy. Loeb, Aron, Schockaert, Uhlenhuth and many others have confirmed and extended this observation, using emulsions, acid and alkaline extracts of fresh and dried anterior pituitary. Eitel, Krebs and Loeser have also shown that anterior pituitary extract will cause hypertrophy of surviving thyroid cells in vitro. Marked hyperplasia of the thyroid, beginning within a few hours, occurs in susceptible animals. This is associated with a rapid loss of iodine from the thyroid and increase in the blood iodine, increase in metabolic rate and increased excretion of calcium and creatin. Exophthalmos also may develop in susceptible species (birds, guinea pigs). It was early pointed out that this symptom complex was strikingly

similar to that seen in exophthalmic goiter. This thyroid stimulating substance is one of several specific hormones of the anterior pituitary (adrenotropic, growth promoting, lactogenic, gonadotropic and possibly splenotropic, parathyrotropic and thymotropic).

The thyrotropic factor has been partially separated from the others by Collip and his coworkers and the chemical and immunological data, while still meagre, indicate that the active substance is probably protein in nature. Sufficient work has now been done with the thyrotropic factor to justify the conclusion that the thyroid may be directly stimulated only by it, irrespective of whether the thyroid stimulation is associated with endemic goiter, with Graves' disease, with compensatory hypertrophy following partial thyroidectomy or with gonadectomy. While the anterior pituitary, therefore, exercises a controlling influence on the thyroid there is evidence that the thyroid exercises equally as profound an influence on the pituitary. Thus the anatomical changes in the anterior pituitary following thyroidectomy can be entirely prevented and cured by giving desiccated thyroid or thyroxine. Studies on the interrelations of the thyroid-pituitary have not appreciably advanced our knowledge as to the cause of myxedema or endemic goiter. The atrophy of the thyroid in myxedema is associated with enlargement of and increase in the thyroid stimulating factor of the pituitary, while in Graves' disease neither pituitary enlargement nor increase in the thyrotropic factor can be demonstrated. The relation of the thyroid secretion to the development of the exophthalmos of exophthalmic goiter has long been a controversial question. Prevailing opinion still favors the view that it is in some way connected with a hypersecretion of the thyroid hormone.

Without going into details regarding the mechanism by which chronic progressive exophthalmos is produced, one may say that in the lower animals the neuromuscular mechanism discovered by Mueller (1858) has not been disputed. In man and in monkeys, which have complete bony orbits and vestigial peri-orbital muscles, there must be the additional factor of weakness of the recti muscles. The first published work on the experimental production of exophthalmos was by Schockaert in young ducks and in the same year by Leo Loeb in guinea pigs following the injection of anterior pituitary extracts and muscles. About this time we reported the occurrence of progressive

exophthalmos in rabbits which developed goiter on a diet of alfalfa hay and oats plus daily injections of acetonitrile. Assuming that the goiter was a manifestation of thyroid insufficiency and that exophthalmos was in some way connected with this insufficiency, we tried thyroidectomy and found that this produced exophthalmos much more quickly. We then tried the effect of pituitary extracts in normal and thyroidectomized guinea pigs and also found that exophthalmos was more easily produced after thyroidectomy than before. The importance of a relative or absolute thyroid insufficiency as one of the factors in the development of exophthalmos seems thoroughly established. Likewise the factor causing the exophthalmos must be present in the anterior pituitary, yet it does not occur in myxedema and cretinism, although both thyroid insufficiency and pituitary hyperactivity are present. Obviously other factors are involved. In the rabbit, and in man too, sex plays a rôle. It is much more frequent in the males, and gonadectomy in the rabbit both lessens the incidence and causes a regression of an existing exophthalmos. It is possible that oestrin is the factor that protects the female by preventing pituitary overactivity. Thyroid therapy is effective both in preventing and in curing this form of exophthalmos in rabbits and guinea pigs (and to some extent in human exophthalmos). Exophthalmos cannot be produced after the sympathetic pathway to the eye has been divided (Horner's syndrome) which indicates that it is dependent upon the stimulation of a sympathetic center in the central nervous system—probably the hypothalamus. The high iodine content of this portion of the brain may be significant in this connection. Thus exophthalmos would appear to be dependent upon an increased irritability of the sympathetic center which is determined by the concentration of thyroxine, thyrotropic hormone, certain salts (Ca, Mg, P) and probably other hormones bathing it. If this should be shown to be the mechanism of exophthalmos production it would be an additional factor in favor of the central action of thyroxine as well as the demonstration of another important thyroid pituitary interrelation.

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Genital Abnormalities

This exceptionally thorough treatment of intersexes was originally conceived by the author as merely a presentation of his own clinical and surgical cases of remarkable genital anomalies, but grew eventually into a complete discussion, embryological, clinical and surgical, of the entire problem of anatomic, pathologic, endocrine and physiologic abnormalities of the sex functions. The bulk of the volume is given over to a complete discussion of hermaphroditism. The twenty cases of true hermaphroditism (one of them reported by the author himself) which have been accepted as proved microscopically are presented in detail. Pseudohermaphroditism, occurring in one out of 1,000 individuals, in whom the gonads of only one sex are present, but the abnormalities of the external genitalia are such that doubt exists as to the true sex, is treated in detail, with many personal case histories. Among the other anomalies discussed are the adreno-genital syndrome, hyper- and hypogenitalism, gynecomastia, hypo- and epispadias, cryptorchidism, and atresia ani urethralis. The volume is beautifully and extensively illustrated with photomicrographs, surgical drawings and photographs. Biologists, physiologists, endocrinologists, physicians and surgeons will find the book of absorbing interest, and should put it on their "must" lists.

—L. H. S.

Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases, by Hugh Hampton Young. xli+649 pp. Baltimore, The Williams and Wilkins Co., 1937. $10.00.

HORMONES OF THE ADRENAL GLAND*

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The adrenals were first described by Eustachius in 1563 but it was not until 1855 that Addison, an English physician, published a clue as to their function. He was able to associate a certain group of symptoms with disease of these glands. Fatigue, pigmentation and digestive disturbances were most prominent. His observations focused attention on the vital nature of these organs. Very soon it was proven by experiments on animals that the adrenals are necessary for life. The next important contribution came in 1894 when Oliver and Schafer demonstrated that an extract of the adrenal produced a marked rise in blood pressure. This was due to a substance obtained from the central part or medulla of the gland. Abel isolated the benzoyl compound of this substance and then Takamine and Aldrich, working independently, isolated the active principle by a method which was commercially feasible. Abel introduced the name epinephrin and Takamine that of adrenalin for this new compound. Its synthesis was accomplished by Stoltz in 1904.

SECRETION OF EPINEPHRIN

One can determine the amount of epinephrin in the adrenals by removing and extracting them, but that gives no information as to the amount normally secreted into the blood stream. This can be determined, however, by collecting the blood as it pours from the gland, and then assaying this blood for its epinephrin content. By cutting the sensory nerves of the region concerned in preparing the adrenal vein for cannulation, it is possible at a later date to carry out this procedure without the use of anesthesia. Inhibition of a contracting piece of intestine is used in the assay of the epinephrin. Satake, Watanabe and Sugawara found that during serene existence 0.00003–0.0001 mg. is secreted per min. per kg. This would amount to 0.4–1.4 mg. per day in a 10 kg. dog. If man secreted a proportionate amount the value attained would be 3–10 mg.

*Aided in part by a grant from The Rockefeller Foundation.

in a day. However, without actual determination we do not know whether such an assumption is justified. Some investigators have obtained higher values than those given by Satake et al. Differences in the method employed as well as the conditions of the experiment may explain the discrepancy. It is difficult to prove that this amount of epinephrin has a physiological effect when secreted in the general circulation over a period of twenty-four hours, although if released at one time the effect would be lethal.

Serenity is often interrupted by stimuli which will increase the output of epinephrin. Exercise as moderate as walking produces an appreciable effect. Cold by its stimulation of sense organs may cause a decided increase. Emotional excitement may have a marked influence. Exposure to heat intense enough to cause a decided rise in body temperature may lead to a seven-fold increase in the output. Hemorrhage in which as much as one-third of the blood volume is lost causes a five-fold increase. Blood pressure maintained at shock level (40 mm. Hg) for one hour or longer will set free a thirty-fold increase. Marked reduction in blood sugar also increases the epinephrin output. Thus insulin evokes an outpouring of epinephrin which in turn raises the blood sugar. This explains the greater sensitiveness to insulin when the adrenal medullae are destroyed. These merely serve as examples of the wide variety of influences which affect the output of epinephrin.

EFFECT OF EPINEPHRIN

The amount of epinephrin secreted under physiological stimulation is enough to produce demonstrable physiological effect. One notes first the change in circulation. The heart is stimulated; blood vessels in the skin, in the mucous membranes and some abdominal organs are constricted, while those in skeletal muscle are dilated. In spite of these effects there is no evidence that epinephrin plays a part in the maintenance of normal blood pressure. Under the influence of epinephrin the spleen forces more red cells into active circulation. Blood coagulation is accelerated. The bronchioles are dilated permitting freer exchange of air with the lungs. Reduction in blood flow and inhibition of movement in the alimentary canal retard digestion. Epinephrin mobilizes the carbohydrates in the body as shown in the diagram (Fig. 1). Blood sugar is increased at the expense of liver glycogen stores while muscle

glycogen is transformed into lactic acid which is later carried to the liver and transformed into glycogen. At the same time the utilization of carbohydrates is increased. When the concentration of epinephrin becomes sufficient general metabolism is increased.

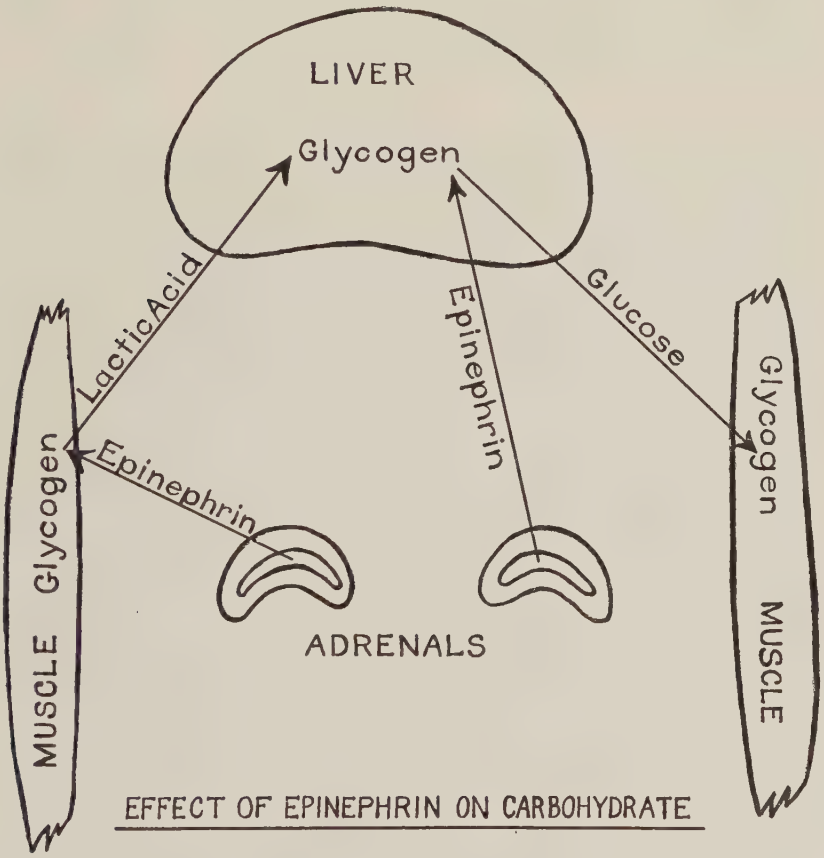

Fig. 1. Effect of epinephrin on carbohydrate.

A careful survey shows us that epinephrin acts on those tissues supplied by the sympathetic nervous system and in the same manner that this system does, stimulating where the latter stimulates and inhibiting where the latter inhibits.

Epinephrin action is fleeting. Any continued effect through its influence, therefore, must be sustained through continued secretion. Thyroxin increases the sensitiveness to epinephrin while thyroidectomy decreases the response as much as fifty per cent.

The total amount of epinephrin in both adrenals of a man is about 10 mg. This much or more may be secreted in 24 hours. Therefore there must be constant renewal. From experiments on animals it has been shown that it is difficult to exhaust the supply. Certain poisons like diphtheria toxin do this most effectively. Severe infections, starvation, convulsive doses of insulin and exophthalmic goiter also cause marked depletion (Corbett).

FUNCTION OF THE MEDULLA

The medulla through its secretion of epinephrin reinforces the action of the sympathetic nervous system. In times of stress its influence is most marked. This led Cannon to propose the emergency theory of the medulla. In the reactions of combat, flight or major emotions epinephrin helps to mobilize the resources of the organism for the emergency. However, epinephrin may influence the organism to a lesser degree in less strenuous states.

TUMOR OF MEDULLA

Occasionally a tumor may develop in the medulla. The symptoms are hypertension, headache, palpitation, perspiration, vomiting, tremor and rapid breathing which most often occur at intervals. The attacks may last a few minutes or longer and the blood pressure rise to 180 mm. Hg or more. Death may occur from pulmonary edema. The release of excessive amounts of epinephrin account for the symptoms produced. Removal of the tumor leads to disappearance of the symptoms. Such tumors have been found to contain much larger amounts of epinephrin than that found in a normal gland.

ADRENAL CORTEX

It has been known for eighty years that the adrenal is vital to the organism, but not until 1917 (Wheeler and Vincent) was it shown that only the outer part, the cortex, is essential to life.

No direct proof of a vital hormone of the cortex was published until 1927, when two groups of investigators, one in Cleveland (Rogoff and Stewart) and the other at Buffalo (Hartman, MacArthur and Hartman) demonstrated that an extract of the adrenal cortex could prolong the lives of completely adrenalectomized animals. The extract prepared by

the second group was free from epinephrin. The hormone essential to life was named interrenalin by the Cleveland group and cortin by the Buffalo group. Beginning in 1930 improvements in the method of preparation were described by Swingle and Pfiffner and by Hartman and Brownell (1). Not only is it possible to maintain the lives of adrenalectomized animals indefinitely with such extracts, but they frequently can be revived from collapse. The first severe case of Addison's

Fig. 2. Shows pigmentation of Addison's disease in contrast to a normal subject. Note the general bronzing with black freckles especially on the face.

disease kept alive by cortin was described by Hartman, Aaron and Culp. He was revived from a comatose condition and survived until he contracted pneumonia nearly eight months later.

In spite of numerous reports to the contrary, cortin has not yet been isolated. The most recent report of DeFremery, Laqueur, Reichstein, Spanhoff and Ulydert claims a highly active crystalline cortical hormone which melts at 180°–182°. Their animal test is not entirely convincing because they used 0.6–2.5 mg. of their substance with added salt in dogs weighing 11–18 kg. Without added salt ten times as much was required.

Swingle and Pfiffner's non-crystalline preparation requires 0.03–0.045 mg. for dogs of corresponding size without added salt. Our best preparation which is amorphous would require 0.011–0.03 mg. for dogs of corresponding size.

All evidence for the existence of cortical hormones depends upon biological tests. So far the only critical test for the vital hormone is the ability to maintain the normal activities of completely adrenalectomized animals. There may be other hormones not yet recognized. This possibility makes it desirable to analyze the responses of normal animals as well as adrenalectomized animals to different preparations from the adrenal cortex.

INFLUENCE ON PIGMENTATION

Although pigmentation never occurs in the adrenal insufficiency of animals it is often present in man (Fig. 2). It may begin at any time in the course of development of Addison's disease or it may be absent altogether. In color it ranges from tan to negroid; occasionally it is gray or olive. The intensity is greatest in regions exposed to light or pressure. Its distribution varies from a uniform shading over large areas to blotches or freckles. It may extend to the mucous membranes. The symptoms of the disease bear no direct relation to the intensity of the pigmentation. Treatment with cortical extract may cause a slow disappearance of pigmentation. Whether pigmentation is due to cortin insufficiency or to the absence of some other substance probably can not be determined until pure hormone is available.

RELATION OF CORTIN TO ELECTROLYTE AND FLUID SHIFT

One of the first signs of adrenal insufficiency is loss of desire for food and water and reduction in absorption from the alimentary canal. This lowers the intake of water and salts. In normal individuals adjustments are made for such reductions without difficulty, the salt and water of the body being conserved through decreased excretion by the kidney. In cortical insufficiency the kidney allows sodium chloride to escape in larger amounts than usual (Fig. 3) so that the body reserve is seriously depleted. The volume of the blood plasma becomes reduced due to loss of water through the kidneys, although at first some of this water escapes into the tissues. Later the tissues also become depleted (Fig. 4). The ability of cortin

to restore the plasma volume without administration of water and salt indicates that the changes are not limited to the kidney. Cortin must bring about a readjustment in the distribution of the electrolytes and fluid within the body itself.

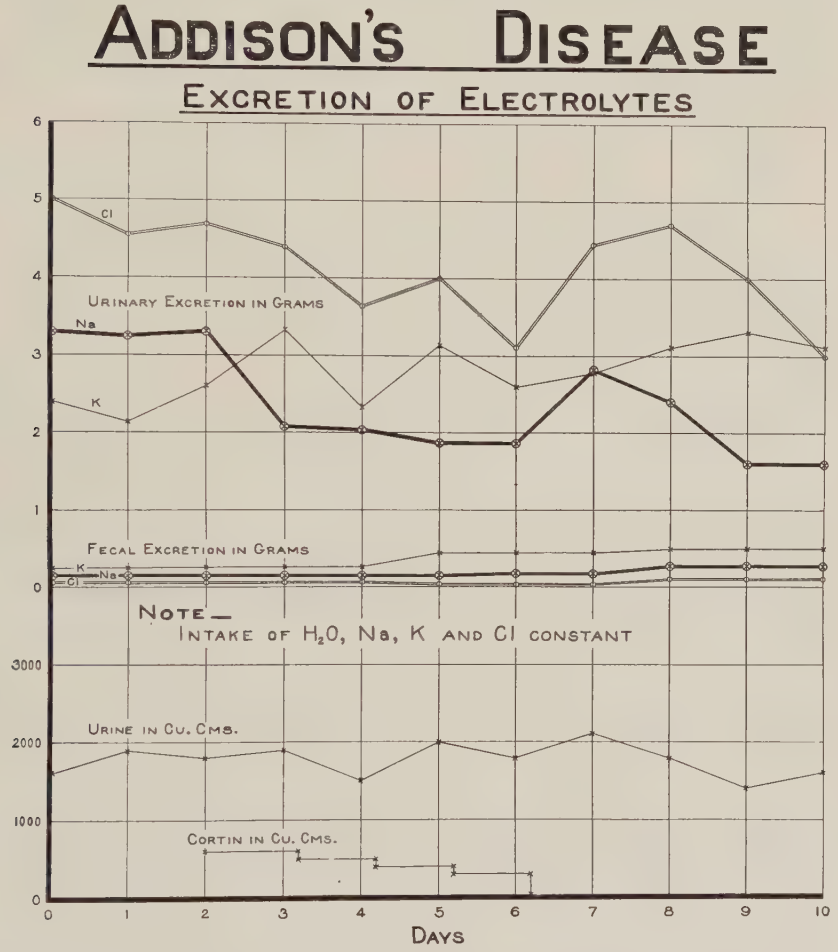

Fig. 3. Renal excretion of electrolytes in a case of Addison's disease. Note that Na and Cl excretion is reduced while the K excretion is increased after cortin injections.

At times it is possible to effect restoration in a subject who is in collapse. However, complete restoration usually requires the administration of water and salt, as well as cortin. Any demand which increases the need for fluid shift is poorly met in

cortical insufficiency. Hemorrhage which may be insignificant in the normal subject may produce collapse in insufficiency. Resistance to heat is much diminished. Water fails to shift as readily from the reservoirs such as skin and liver, resulting in less available water for evaporation and heat loss. Cortical insufficient subjects develop serious symptoms and succumb more readily to heat than do normals (Hartman, Brownell and Lockwood).

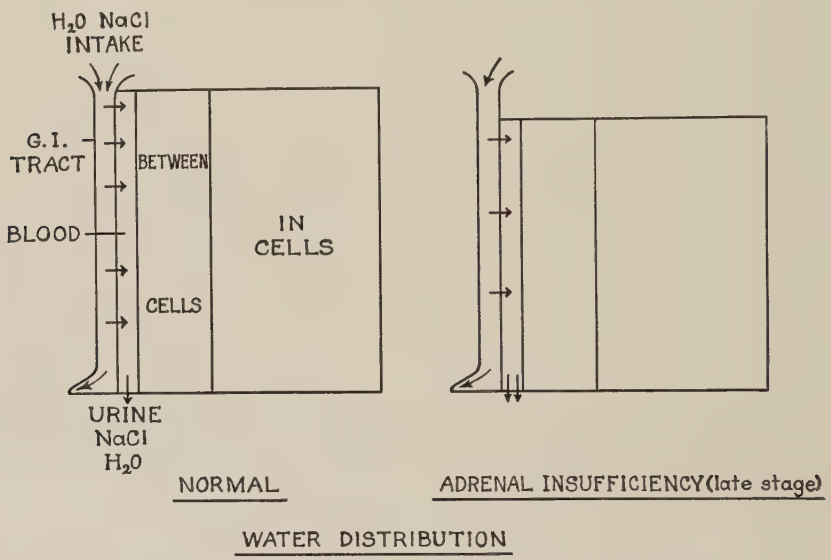

Fig. 4. Distribution of water in well established adrenal insufficiency compared with the normal.

Increase in the NaCl intake may ameliorate the symptoms of early cortical insufficiency but it is unavailing in the late stage. Cortin not only enables the kidney to maintain the threshold for electrolyte excretion which exists under normal conditions, but when injected into normal individuals in large amounts raises the threshold above normal for NaCl but lowers that for potassium. These effects persist for several hours following a single injection.

Sodium chloride depletion in itself may cause the development of symptoms (McCance). These are weakness, lassitude, cramps and severe cardio-respiratory distress on exertion.

RELATION TO THE NERVOUS SYSTEM

In adrenal insufficiency whether experimental or pathological (Addison's disease), symptoms develop which indicate marked changes in the nervous function. Not only does fatigue come on more easily but there is disinclination to muscular or mental effort. Loss in interest in surroundings may lead to a state of inertia which verges on coma. On the other hand the subject may be easily irritated and may even become disoriented. The cerebral manifestations especially in the late stage of Addison's disease may be treated by the psychiatrist without recognition of the disease. The insomnia, exhaustion, incompetence and confusion are no different than may appear in conditions not involving the adrenal. The administration of cortical extract corrects these conditions when due to cortical insufficiency. The effect might be the result of action on some primary function which indirectly influenced the nervous system such as the distribution of electrolytes or it might be due to direct action on the nervous system itself. However, observations of Hartman and Lockwood seem to show that cortin affects the reflexes directly because they become more readily fatigued in adrenalectomized rats without cortin than in similarly operated animals with cortin. This hormone influences the nervous system in conditions without obvious adrenal insufficiency. In some cases in which there is organic neurological change cortin improves the motor functions and the mental status. Fatigue is diminished with a concomitant increase in strength. Myotonic manifestations and fibrillation, when present, are decreased. A sense of well-being replaces depression and irritability disappears. (Hartman, Beck and Thorn.) Normal individuals at times respond, the immediate effect being drowsiness and release of nervous tension. These effects are not due to suggestion because sheep in a state of neurosis due to overtaxing the nervous system in conditioned reflex experiments, show marked improvement under cortin therapy. (Liddell, Anderson, Kotyuka and Hartman.) This neurosis is characterized by extreme excitement, uncooperative behavior and spontaneous nervous twitching movements of the limb concerned in the reaction. Administration of cortical extract increased the vigor of the conditioned reflex and decreased the frequency of the nervous movements. The improvement persisted for more than three weeks after the

last injection. Increased resistance to fatigue, which persisted longer than 47 days after cortical extract injections were discontinued, had previously been observed in a patient with muscular dystrophy (Hartman and Thorn). The assumption is made that cortin is responsible for these effects.

EFFECT ON METABOLISM

Metabolism is lowered as much as 25 per cent in cortical insufficiency. In other words the sum of the chemical changes in the body is reduced that much under basal conditions. When there is stress the difference is augmented. Upon exposure to cold adrenalectomized animals may produce the extra heat required for a short time but this finally fails so that the temperature drops. Reflex activity is involved in the reaction to cold. It is possible that eventually the failure of the body musculature to produce more heat is due in part to fatigue of these reflexes as well as to depleted carbohydrate reserves. In adrenalectomized animals not exposed to cold there is a reduction in carbohydrate stores. This is not entirely accounted for by the lowered food intake because a twenty-four hour fast causes almost complete disappearance of liver glycogen in operated animals but not in normal animals. The blood sugar of the operated animals is also lowered. Muscle glycogen eventually falls. Adrenalectomized dogs whose electrolytes are maintained with cortin or without cortin by the administration of large amounts of sodium salts show a decided fall in blood sugar (Harrop et al.). This suggests that there may be another hormone which is concerned with carbohydrate metabolism. Such a view is supported by Long, who found that cortin did not maintain diabetes undiminished in adrenalectomized-depancreatized cats. We (Hartman and Brownell (2)) have been able to maintain the high blood sugar and sugar excretion in the urine in similar fed animals by large amounts of cortin provided the animals had not lost too much weight. In a fed dog with both adrenals and pancreas removed it has also been possible to maintain the high sugar values with cortin but the ketosis was much diminished (unpublished work of K. A. Brownell). The enlargement of the cortex produced by injections of insulin (Riddle) also gives evidence of a relation of the cortex to carbohydrate metabolism.

Cortical extract has an effect on respiratory metabolism in normal individuals according to observations of Hitchcock

and Grubbs in our laboratory. It reduces the oxygen consumption under conditions requiring more oxygen as in moderate exercise. The average reduction in eleven subjects was nearly 6 per cent during standing and about 14 per cent during walking. This seems to indicate an increase in muscular efficiency. The effect persists for several days after the extract is discontinued. This persistence reminds one of the after effect in neurotic sheep and in occasional patients. (See nervous system.)

VITAMINS

It has been known for a long time that the adrenal cortex hypertrophies in vitamin B_1 and C deficiencies. Another suggestion of a relation between the cortex and vitamin C is the observation that in late stages of adrenal insufficiency hemorrhages may occur from the gums and in the alimentary canal, a condition similar to that found in scurvy. We (Lockwood and Hartman) have studied the effect of cortical extracts in deficiencies of these vitamins. In the preparation of extract ethyl ether was employed at one stage to avoid inclusion of vitamins B^1 and C which are found in the cortex. These vitamins are insoluble in ether (Sherman and Smith). Additional evidence of the absence of vitamin C was obtained by the spectrographic method (Lockwood, Swan and Hartman).

Injection of cortical extract delayed the weight loss and postponed the onset of signs and symptoms in both avitaminosis B_1 and C. In order, as we thought, to reduce the active adrenal tissue we removed one adrenal in some animals. The results were just the reverse of what was expected. On both the B_1 and C free diets such an operation produced an effect similar to the injection of cortical extract. However, this did not occur if we waited about three weeks after the adrenalectomy before starting the vitamin free diet. It seemed that there was an overproduction of this ameliorating substance in the remaining adrenal for about three weeks after the operation.

Extract is most effective early in the avitaminosis when some vitamin from the pre-experimental period is still available in the organism. It is also more effective when a partial protective amount of the vitamin is fed. These observations suggest that cortical extract aids in the utilization of vitamins B_1 and C. Our extract contained significant amounts of cortin as judged by tests on adrenalectomized animals. Cortin or some unknown substance in the extract must have been responsible for the effects in vitamin deficiencies.

CORTILACTIN

Adequate amounts of cortical extract enable adrenalectomized animals to give birth to young. Some time ago we (Brownell, Lockwood and Hartman) reported that cortical extract could be divided into two fractions, one containing cortin and the other a substance (cortilactin) necessary for lactation. It was possible to make this separation only under certain conditions. Cortex was extracted with 90 per cent alcohol. After removing the alcohol by vacuum distillation from the resulting extract the residue was taken up with ethyl ether. Ether was removed in vacuo from the ether extract. The residue was extracted with 70 per cent alcohol. The resulting solution was chilled to $-12°$ C. The lipids which were precipitated contained the factor necessary for lactation. Cortin remained in solution. Ordinary methods of preparing cortical extract do not separate the lactation factor from cortin. Cortin alone does not seem to enable adrenalectomized rats to lactate sufficiently. If cortilactin is added or if it has not been separated from cortin in the preparation of the extract, lactation is well supported. A positive effect on milk secretion has been obtained in the human being with cortilactin (unpublished work of Thorn and Hartman). Eight patients carefully controlled in the hospital have been studied. All were secreting very inadequate amounts of milk. Six of these showed increased milk production within 48 hours after starting the injections. The remaining two developed the typical sensation of tingling in the breast but no milk secretion. In one of the patients who responded with increased milk secretion, the amount of milk secreted fell to zero after cortilactin was discontinued.

CORTIPRESSIN

Although the blood pressure of adrenalectomized animals is maintained by cortin, in some cases of Addison's disease seemingly adequate cortin treatment often does not re-establish the normal blood pressure level. Therefore it is possible that an additional factor is lacking. Looney and Darnell have found that a glycerol extract of the adrenal cortex administered by mouth in the human-being causes a prolonged increase in blood pressure. The marked rise occurs after four or five days and disappears in ten to fourteen days after withdrawal. The active substance is insoluble in fat solvents and is more

stable toward alkali than is cortin. They have named the substance cortipressin. We have employed a glycerol extract of the cortex in the treatment of Addison's disease but the effect on blood pressure is not striking.

ADRENOSTERON

Reichstein has isolated a compound which has about one-fifth the potency of the male sex hormone, androsteron. He calls the new compound adrenosteron. Frequently tumors of the adrenal cortex are found in cases of abnormal masculine development. Young boys so affected are precocious in both growth and sexual development. Females so affected change to the masculine type. The distribution of the hair and the character of the voice change, while menstruation ceases if it has begun. Removal of the tumor is followed by reversion to normal. Excessive production of adrenosteron might explain the changes resulting from cortical tumors.

CONTROL OF THE ADRENAL

Although the adrenal is well supplied with nerve fibers, their influence seems to be confined to the medulla. How is the cortex controlled? Within six days after hypophysectomy the adrenals of the rat are reduced to one-half the weight of the controls; maximum atrophy is reached in thirty days. This is largely due to changes in the cortex. All zones show marked reduction in the cytoplasm (Smith). The atrophied cortex still produces the vital hormone for if removed the animal dies of adrenal insufficiency. However, its production is probably inadequate because symptoms of cortical insufficiency develop from hypophysectomy. In hypophysectomized rats removal of one adrenal does not lead to hypertrophy of the remaining gland as it does in normal animals (Reiss, Balint and Aronson). Pituitary preparations restore degenerating adrenal cortex or, in normal animals, can increase the size of the cortex as much as two-fold (Emery and Atwell). Thus it has been demonstrated that the pituitary plays a major role in cortical control through its production of the adrenotropic hormone.

RESPONSE OF THE CORTEX TO STRESS

It is well known that in adrenal insufficiency there is greater susceptibility to infections, toxins, cold, heat, exercise and trauma. In order that these conditions be met considerably

more cortin is required. Cortin, therefore, has an emergency function as well as a sustaining function. Various stresses if repeated with sufficient frequency can increase the weight of the adrenals. Examples are shown in Fig. 5 in which the relative adrenal weights of the adrenals of rats under stress are

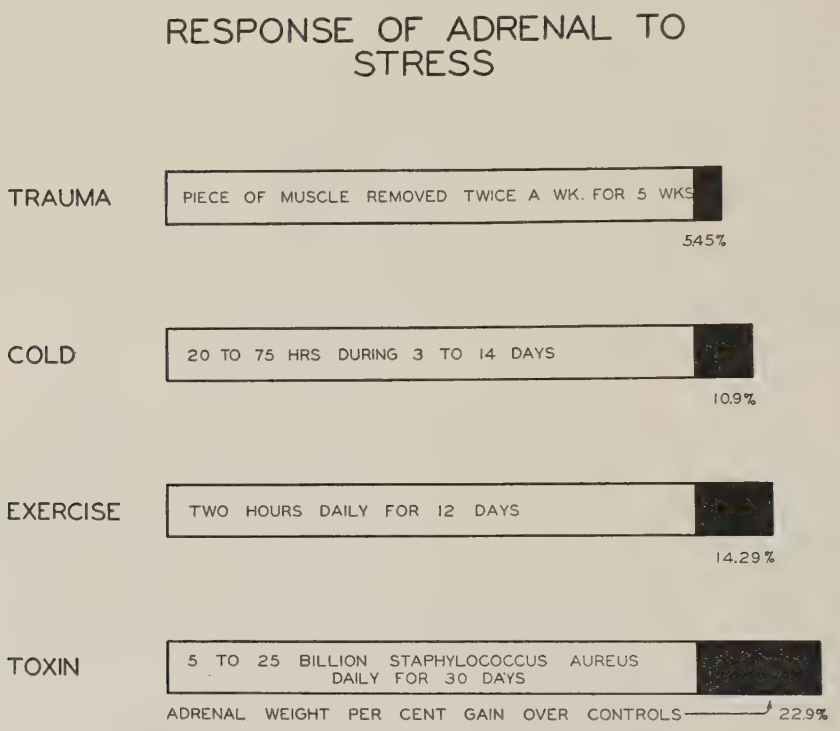

Fig. 5. Response of adrenal to stress (rat), gain shown in black.

compared with control litter mates. The cortex is largely responsible for the increase in weight.

Although a part of the adrenal tissue is adequate to maintain the organism under quiet conditions, stress requires the functioning of all of the adrenal tissue. Rats with one adrenal removed are unable to produce as much heat when exposed to cold as when both adrenals are intact. For this reason they do not withstand cold so well (Horvath), Fig. 6.

COMPENSATORY HYPERTROPHY

If adrenal tissue is destroyed by disease or other cause, does the remaining tissue have the power to regenerate and if so can it replace the amount of tissue lost? The need for reserve adrenal tissue in stress makes this a very important question.

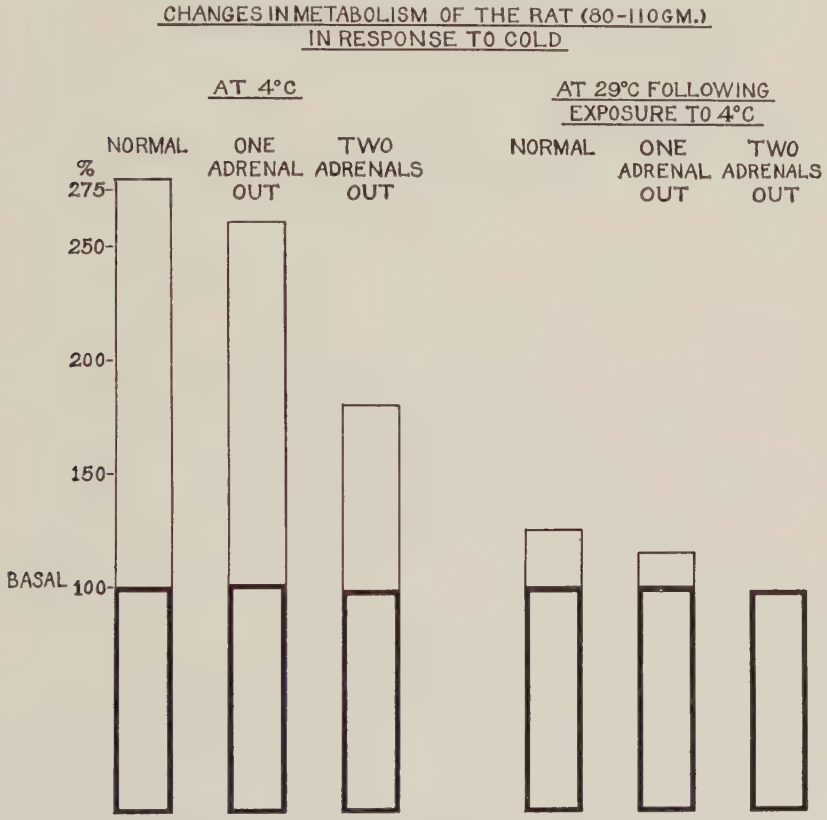

Fig. 6. Changes in metabolism of the rat in response to cold.

The failure to find evidence of regeneration of adrenal tissue at autopsy in Addison's disease may be explained by the assumption that had there been regeneration the patient would not have come to autopsy. It seems necessary to use animals to test the possibility of hypertrophy.

In young rats removal of one adrenal results in the hypertrophy of the remaining gland on the average of sixty per cent. (MacKay and MacKay.) This is far short of compensation.

Destruction of part of the adrenal tissue by cautery in cats is not followed by significant hypertrophy (Hartman). It is possible that the development of scar tissue from cautery prevented regeneration. Therefore, experiments were per-

TABLE I

Sex	Time (Days) Elapsed After		Body Weight		Weight of Adrenal	
	First Operation	Second Operation	Original gm.	At End gm.	Right gm.	Left gm.
F	126	64	2050	1340 (died)		0.055 0.044 0.099
M	401	281	3675	4260	0.175	0.112 0.125 0.237
F	329	268	1800	2380	0.121	0.055 0.089 0.144
F	333	216	1475	2225	0.114	0.063 0.038 0.101
M	354	294	1995	3100	0.149	0.067 0.104 0.171
F	399	282	2650	3150	0.245	0.168 0.119 0.287
M	399	281	3300	3880	0.160	0.086 0.075 0.161

formed in which part of the left adrenal was removed by a sharp scalpel. The piece removed was measured and weighed. Months later the right adrenal was removed, measured and weighed. From two to nine months after removal of the right adrenal the remainder of the left adrenal was removed, measured

and weighed, the accompanying table (Table I) presents the results. The weights of the first and second pieces of the left adrenal were added together. A comparison of this sum with the weight of the right adrenal shows that there could not have been a great amount of regeneration if one assumes that the right and left glands are not greatly different in size. The piece remaining in situ never regenerates enough to compensate in size for the tissue removed. When accessory adrenals are present in those animals which survive for a considerable time following adrenalectomy, the accessories do not become very large. In four cats the largest which we have observed (300 days after complete adrenalectomy) has been 55 mg. We are forced to conclude that although a small amount of regeneration of adrenal tissue takes place, there is never complete compensation.

TABLE II

Hormones	Function
Epinephrin	Reinforces sympathetic nervous system.
Cortin	Maintains electrolyte balance.
	Required by nervous system.
	Aids in utilization of Vitamins B_1 and C.
	Necessary in metabolism of carbohydrate and fat.
Cortilactin	Required for lactation under certain conditions.
Cortipressin	Raises blood pressure.
Adrenosteron	As male sex hormone

CONCLUSION

Two hormones of the adrenal are definitely established. One, epinephrin, is the only hormone indicated from the medulla. The other, cortin, is but one of a number indicated from the cortex (Table II). The function of cortin is somewhat indefinite. It maintains electrolyte balance and seems to be required by the nervous system. It may be the factor which aids in the utilization of vitamins B_1 and C. Some other factor in addition to cortin seems to be necessary for the metabolism of carbohydrate and fat. Other provisional hormones are cortilactin, cortipressin and adrenosteron. Further purification of the factors in the cortex will be required to establish some of them as hormones.

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Religion

This volume is the twenty-fourth edition of a popular book by a scientific man, a book on religion by the director of the Psychological Service Center of New York. As these many editions were issued in a year and a half, the book may fairly be classified as a "best seller." Dr. Link tells how, as a practising psychologist, he found that the greatest lack in the personal development of masses of people consisted precisely in the lack of a purpose, of an ideal, such as religion would give them. Thus, without entering into the philosophical problem of the existence of God, he found the Bible to be the best text-book extant on morality and character development. In his own words: "Psychology differs from all other sciences in this important respect. Whereas the other sciences have taught us that our beliefs about nature were wrong, psychology is proving that many of the ancient ideas and precepts about the development of a good character and personality were right." Dr. Link's own work is in the field of individual psychology, though he works through general means of adaptation and attacks the psychoanalysts with real bitterness. When he applies his ideas, however, to the field of education and of social reform, many of us would differ with him, on the ground that his conclusions do not follow from his personality studies, mental testing, and similar work in an unrelated field. He holds, for example, that education tends to delay character development rather than advance it because it makes the pupil dependent on the teacher. In the same way he objects to extension of government services as making individuals less self-reliant, whereas some of us feel that starvation is more immediate than character development.

—Lee J. Levinger.

The Return to Religion, by Henry C. Link. New York, the Macmillan Co., 1936. $1.75.

THE HORMONES OF THE ANTERIOR PITUITARY

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INTRODUCTION

This Society—"devoted to the promotion of research in science"—may very reasonably ask a speaker to begin his address with a statement of the general or wider meaning of current advances in the field for which he is to speak. Perhaps the usefulness of such a general statement tonight is increased by the circumstance that the present discussion concludes a symposium of 10 lectures on Hormones which this Chapter of Sigma Xi has been resourceful enough to arrange and present within the year. Again, those several earlier and related discussions can very notably reinforce any general statement which might be made concerning advances in the study of the anterior pituitary hormones alone.

Almost too obvious to require mention in such a general statement is the practical certainty that present and future advances in our knowledge of the hormones will make medicine more effective in dealing with at least several diseases and incapacities of man and animals. But rightly notable here, because rather less evident, are two somewhat related things: First, some conditions not classifiable as disease but as subnormal developments of body or mind—such as small stature and some forms of dull mentality—will probably prove more amenable to favorable influence by hormones than from any other therapeutic source. Second, the hormones have already provided the essential basis for an understanding of the cycles and reproductive adjustments peculiar to women, although 15 years ago not one of the several hormones involved in the production of those cycles had been isolated or suitably measured. Another 15 years should add very useful elements of control to our present quite gratifying degree of comprehension of those cyclical adjustments to which one-half of mankind is subjected during much of the span of life.

Further—and this point is of interest to investigators in all branches of science represented in this Society—advancing knowledge of the hormones is enabling us to begin to see and comprehend the mechanisms by which our own complex bodies

maintain their own internal environment at a constant or steady state. Moreover, some of these hormones have even shown themselves to be the means by which certain peculiar aspects of this steady internal state is sometimes greatly upset or changed —likewise to the great advantage of the organism—and all this supplies hitherto missing information on the great problems of biologic organization and adaptation.

Precisely this last-named gain—a gain on a scientific and philosophical question which has long seemed troublesome to some scientific men—has such exceptionally wide application in the sphere of thought that it deserves a central position in this introductory statement. The knotty problems of adaptation and complex animal organization—particularly that of the brain and the regulatory processes of animals—have been thought by some biologists and philosophers to be best accounted for by the assumption of a guiding vitalistic force, a force essentially divorced from matter and akin to the supernatural. As the profound and peculiar regulatory powers of the hormones have become even partly known—particularly since these non-nervous chemical agents have been found to constitute an additional regulatory mechanism affected by both the nervous system and the external environment—the bases of the doctrine of vitalism have been sapped and severely shaken. The newer outlook conforms well with the naturalism so well stated by Darwin in his great study of 1874. And we are encouraged to proceed on the conception that an organism is to be understood, if at all, in terms of its organization, its environment, and its past. Up to now the supernatural has disclosed no sphere or place of its own in organisms.

In calling attention to these broad or general contributions of endocrinological research one should at once note that many other branches of biological or life-science are making similar, perhaps equal or greater, contributions to the present and future well-being of man. Personally I like to think of the sum of all this biological research as affording full justification for the opinion and statement of a great mathematician and chemist who for a generation was president of Harvard University and perhaps America's greatest educational leader. Near the end of his service at Harvard, President Charles W. Elliot said: "The human race has more and greater benefits to expect from the successful cultivation of the sciences which deal with living things than from all the other sciences put together."

Now lest some of my audience at once write me down as an incurable optimist, supremely satisfied with all that is labelled biological, I must add another general statement—and admission. It is this. Though our laboratories of endocrinology and of a dozen other divisions of life-science have all done well within their walls, they have failed in most of the world that lies outside those walls. The thoroughly biological thing that counts is man, the citizen—the walking, sleeping, or perhaps just now, the "sit-down" citizen; and, the future citizens now in public or other schools. These—our present and future citizens—are now left largely untouched by the best products of our biological laboratories. *We learn; but we have established only slender channels to the great stream of the mental life of modern man.* Within the time of men now alive we have learned the broad outlines of man's own nature and man's place in nature; but the citizen is unaware, and the future citizen remains practically untaught. Our very best contributions are to the mental orientation of men—yet any such contribution whatever is contingent upon contact and possession and these are not yet achieved. The laboratories have won only Pyrrhic victories until secondary schools—the only broad path to our people—begin the task of carrying basic biologic truth to our future citizens.

From these very general and introductory reflections concerning endocrinology and its biological settings we may next turn to a consideration of some quite general aspects of present knowledge of "the hormones of the anterior pituitary."

GENERAL CONSIDERATIONS

At this stage of high uncertainty concerning most that pertains to "anterior pituitary hormones" no one would elect to speak or write on that subject. You are asked to understand clearly that I have had no choice; I was drafted, and I am still reluctant. There would be only pleasure in placing before you such observations and measurements concerning some *responses* to pituitary products as have been recently accomplished in our own laboratory; but there is real danger that some opinions on pituitary hormones which I am now forced to put on record will be proved wrong even before the end of the present year. Our actual knowledge of the *hormones*—the elaborated active molecules—of this remarkable gland is so fragmentary that even our first words on the subject must include opinion and specula-

tion. Sensing the harsh and speedy fate that awaits at least some of the speculations which must be set down in the first section of this communication I note that those paragraphs are to be regarded as my own particular view of this subject on this particular day.

To a highly significant degree the hormones of the anterior pituitary have been found to exert their action upon other hormone-producing organs. It now appears that the chief function of the pituitary is to regulate the production of chemical regulators (hormones) in other endocrine glands. The effects of pituitary hormones upon the several glands and processes of the body are both numerous and impressive. Though these effects or responses are as yet imperfectly known, and though several known responses can not yet be definitely assigned to a particular hormone, many responses have been and are now being studied with notable success. As already suggested, however, much less success has attended efforts to learn either the true number or the chemical structure of the pituitary hormones themselves. None of them has been isolated in a satisfactorily pure state; and some of the imperfect isolations accomplished from dead pituitary tissue may represent only fragments of those molecules (hormones) which pituitary cells normally release from their surfaces. These uncertainties as to the number and the chemical structure of A. P. hormones, like the now recognized difficulties encountered in their isolation and purification, are bound up with their probable protein (or polypeptid) nature and with the further complicating circumstance that more than one hormone is produced in the gland; indeed we are faced with a serious probability that more than one hormone is produced by one and the same type of pituitary cell, or even by the same cell.

While speaking of these uncertainties and probabilities we may as well discuss a possible way of regarding the production of a seeming multiplicity of hormones, or of hormone fragments, from two types of secreting cells. Much cytological study of the anterior pituitaries of higher vertebrates indicates the presence there of three special types of cells—chromophobes, eosinophils and basophils—and that only the two last-named types show secretory activity. Again, studies of responses to pituitary hormones or hormone-fragments, and also vague indications obtained from methods of isolating these pituitary products, provide some basis for grouping most or all of the secreted

products into *two* groups. Thus the eosinophil cells would seem to be the source of a prolactin-adrenotropin product; and this substance probably elicits not only the responses already credited to these particular names, but also those responses designated as diabetogenic and ketogenic (and *growth* also in some animals). The basophils would seem to be the source of follicle-stimulating hormone (FSH) and probably for luteinizing and such other gonadotropic hormones or hormone-fragments as may exist (a gonadotropic contribution to the body *growth* of some animals seems also probable). Whether the thyrotropic hormone is of eosinophilic or of basophilic origin now seems only a hazardous guess. But, besides its specific capacity to stimulate the thyroid gland there is also reason to assign growth-promoting capacity (in at least some animals) to this hormone. The conception thus briefly stated requires further immediate comment.

On this view the writer does not find it necessary to allocate a "growth" hormone to either type of cell, since he believes that the unquestionable ability of the pituitary to promote bodily growth really rests upon the aggregate of helpful things contributed by other (perhaps all) pituitary hormones. This view also very definitely assigns to different pituitary hormones unequal growth-promoting rôles in different animal species—e. g., prolactin has been found of chief importance to growth in the pigeon (1, 2); thyrotropic seems of chief importance in the dwarf mouse (3); while no pituitary hormone is required for continued normal growth in some of the lower vertebrates. Again, removal of the pituitary gland (and all of its hormones) in the young rat of 25–35 grams scarcely interferes with its growth until after it reaches a weight of about 60 grams (4); and, the same "growth" extract that will promote growth in normal female rats from the 4th to 10th week of life will or may fail to promote such growth in similar male rats (5). Sex difference as well as species difference is concerned therefore in the growth response of an animal to products of pituitary origin. Of course Evans (6, 7, 8) long ago showed that adult male rats whose growth curves have plateaued can be made to grow with alkaline pituitary extracts. Finally, it is to be noted that in high degree the pituitary hormones (or hormone fragments?) have shown augmentation or synergistic actions upon each other; and one such synergism of the growth response has been observed (3) in the dwarf mouse and another on basal metabolic rate (2)—with prolactin (or prolactin-adrenotropin) and thyrotropic apparently here serving as members of the synergistic pair.

It was indicated above that the product (or products) of eosinophil cells yield many responses—those associated with prolactin, adrenal repair, glycosuria, ketosis, and a rôle in growth. The eosinophilic contribution to the growth response, in most animals, probably exceeds that of the basophilic product. Is more than one eosinophilic product liberated by the living cell? Unless thyrotropic hormone, in addition to prolactin, is of eosinophilic origin I do not think that present evidence compels us to accept even a duality of normally liberated eosinophilic products. Though there is non-negligible evidence for the existence of an adrenotropic hormone, cortical repair—like growth—may yet prove to be a response to other hormones, even involving a synergistic action of these, and not a response to a single entity. Again, it is perhaps conceivable that the structure liberated by the eosinophil cell is a molecule holding prolactin and adrenotropin in combination, and that this molecule is split into parts by the means used for their seeming (partial) isolation from the dead pituitary tissue (see below). Certainly some fragmentary information, particularly that dealing with pituitary influence on carbohydrate metabolism, suggests a close association—perhaps interrelation is the better word—of adrenal maintenance on the one hand with some of the responses to prolactin on the other.

The basophilic product—a gonadotropic complex—is probably responsible for a specific stimulation of *growth* in gametogenic tissue and in interstitial tissues, besides inducing a transformation (luteinization) of granulosa or of thecal cells of female mammals into useful but fated luteal cells (or is the latter process mediated by products originating in adrenals, gonads, etc.?). The number of hormones, or of hormone fragments, involved in regulating these responses is not clear. The status of FSH as a definite normally released product of the pituitary is conceded by all investigators. The almost complete separation of two fractions having gametogenic (FSH) and luteinizing (LH) properties has been reported by Fevold, Hisaw *et al* (9) and Wallen-Lawrence (10). Evans *et al* (11) report still other active fractions; and Smith, Engle and Tyndale (12) report fairly complete separation of one principle (LH) from pregnancy urine and another (FSH) from castrate and menopausal urine.

Since pituitary *hormones*—not *responses* to pituitary products—are the subject of this paper we must further pursue these considerations. Not only may our extraction methods pick up

unfinished hormone fragments from the interior of dead pituitary cells; these methods—in addition to their known capacity to inactivate (more or less rapidly) the true hormones themselves—are perhaps also capable of both physically *separating* and of *chemically changing* two or more of the fragments that should form a molecule of a true hormone. It is improbable, though conceivable, that some apparant synergisms among pituitary products may rest therefore upon the chance given such fragments to recombine (when later put simultaneously in the blood stream) and form more of the true hormone. On *a priori* grounds there is a fair probability that some of these fragments of hormones have physiological activity, but physiological activity that is not identical with that of the entire molecule (hormone) which is normally liberated by the living pituitary cell. If this is true, our pituitary "extracts" contain a greater number of active products than of products to which the name hormone properly applies.

From what has just been stated it is clear that some importance attaches to the fact that certain pituitary hormones have been recovered from the blood. Though present failure to find certain pituitary products in the blood stream does not declare that such products are not normally liberated from the secreting pituitary cells—and therefore not true hormones—the short list of hormones that have been so recovered deserves mention.

Prolactin has been reported in post-partum human serum by Tesauro (13); our laboratory has detected it in the serum of pregnant mares, and Leblond (14) found it also in the serum of lactating mares. Geschickter and Lewis (15) found notable quantities of prolactin in cystic human mammaries and in the mammaries of post-partum cows. Leblond and Noble (16) find traces in whole fish liver and brain, and Bates and Riddle (unpublished) confirmed this result with pigeon liver. Part, but not all, of these results were obtained by the extraordinarily sensitive *local* crop-sac test of Lyons and Page (17); it is doubtful whether a test equally as sensitive as this latter test is now available for any other anterior pituitary product. Moreover, the implantation of intact untreated pituitaries of pigeons (Riddle and Schooley, 18), of fowl (Burrows and Byerly, 19) and of rats (Reece and Turner, 20) has permitted the detection of prolactin in all these untreated glands.

Follicle-stimulating hormone (FSH) is well known to be present in large quantities in the serum of mares during most of

the term of pregnancy (Cole and Hart, 21). Many studies have indicated the presence of this hormone in human blood during pregnancy, and after castration or the menopause. Again, the implantation of intact untreated pituitaries of mice and rats—in the classic experiments of Smith and Engle (22) and Zondek and Aschheim (23)—supplied the original evidence that this hormone exists in the pituitary.

Luteinizing hormone (LH) extracted from urine and placenta seems to differ from that of pituitary origin. Hellbaum (24) reports the isolation from mare serum of an LH which is similar to pituitary LH. Again, the implantation of untreated pituitaries produced luteinization (22, 23)—though this alone does not establish the existence of a luteinizing hormone of pituitary origin.

Thyrotropic hormone apparently has not been satisfactorily demonstrated in the blood—probably because a sufficiently delicate test for minute amounts of it have not yet been developed. A few cc. of mare serum—very rich in FSH—were found incapable of affecting the metabolic rate of doves (2). But implantation of surviving anterior lobe to the vicinity of the thyroid has supplied evidence of the capacity of such tissue to stimulate the thyroids (Atwell, 25; Etkin, 26).

Other alleged pituitary hormones can not here be given a similar individual survey. But we note our opinion that evidence of the types (and in the volume) so easily cited for prolactin and FSH is not available for the several alleged entities: growth, adrenotropic, diabetogenic, ketogenic, fat metabolism, antagonist, interstitial cell stimulating, pancreatropic and parathyrotropic. It is true of course that less sensitive tests may have interfered with positive findings in these cases. The growth response in rats has indeed been obtained from untreated rat (and pig) pituitary implants (Smith, 27; Smith and Dortzbach, 28); but on the point here in question that result is quite indecisive since other data suggest that the growth response rests upon the sum of helpful things contributed by more than one pituitary hormone. Smith (27) was the first to show that the thyroid hormone (desiccated thyroid), added to "growth" hormone, could cause more rapid growth (hypophysectomized rats) than did the growth extract alone.

Some at least of the above list of "alleged entities" almost certainly rest upon the wholly unsubstantial basis that the injection of a pituitary extract was followed by a particular

response, this response thereafter gratuitously supplying a name for an imagined product in the pituitary—whereas the response may in fact rest upon (a) a hormone produced in any such organ as the thryoid, gonad, adrenal, pancreas, liver, or indeed (b) upon a combined action of hormones produced in several of these organs; or, again (c), some responses thus translated into entities may rest, in part at least, upon the contamination of true anterior lobe hormone by effective amounts of intermedin or posterior lobe hormones. Few things are easier than to find a hitherto unrecognized response to the administration of mixed pituitary extracts; and few things are more difficult than to prove that the new response is produced by a hitherto unrecognized specific anterior pituitary product.

It is against the background of the preceding discussion that, for the present, it seems helpful and possible to think of two groups of substances elaborated by the pituitary; and also possible to associate the one group with the eosinophils and the other with the basophils. Since cytological phenomena within both these types of cells show waxing and waning aspects of the process of hormone formation (secretion) it seems possible that the effective molecules formed while the cell is being forced to halt secretion is not the exact equivalent of that formed under conditions which accelerate its secretory activity (thus recalling the production successively of estrone and progesterone by the same ovarian cell—or from a derivative of it). Though this concept has no experimental basis it would permit us to rationalize the production of more than one (chemically related) hormone in the same cell or type of cell. A gonadotropic chemical relative(s) of FSH, or even thyrotropic hormone, might thus arise from the basophil; again, perhaps prolactin-adrenotropin and thyrotropic might come from reverse phases of the functioning of individual eosinophil cells—some of which are in regressive phase at the moment others are highly active.

We here recall that though one is forced to speculate there should be an end to it. It is now an observed fact that an element (light) of the external environment (Rowan, 29) and the nervous system (Friedgood and Pincus, 30; Haterius and Derbyshire, 31) both share in regulating the output of at least some pituitary hormones (FSH). To this must be added important facts indicating that the production of certain pituitary hormones is affected by the output of other pituitary hormones or by secondary products of the action of a pituitary hormone. Thus a

release of gonad-stimulating hormone leads to a stimulation of sex-hormones (estrone, testosterone) and these usually so act upon pituitary cells as to check or suppress the further release of FSH (Moore and Price, 32; and others), while the estrone induces a release of LH (Hohlweg, 33; Fevold, Hisaw and Greep, 34). Again, it is reported (Bates, Riddle and Lahr, 35) that prolactin (an eosinophilic product) is capable of suppressing the release of FSH (a basophilic product) in mature birds. These few instances of means of control of pituitary hormone output have wide biological significance since they permit us to begin to see the regulatory mechanism for some of the most intricate aspects of biologic organization and adaptation.

SOME RESPONSES TO SPECIFIC HORMONES

We may now consider briefly certain results recently obtained in our own laboratory which have bearing upon some of the general views already discussed. We first examine some results dealing with relationships of the prolactin-adrenotropin component (of eosinophilic origin) to carbohydrate and fat metabolism and to growth.

Data of Riddle and Dotti (36; and unpublished) show that in pigeons, doves and rabbits (apparently not in rats) the *blood sugar* is increased by injecting these animals with prolactin. Table I gives some typical findings on pigeons.

Most of the preparations used in these studies were in fact called prolactin; but certainly some of those preparations (not Nos. 380, 394H) had power to enlarge the adrenals of 21-day old rats or partially to repair the adrenal cortex of hypophysectomized pigeons. These cortical responses have been assigned to a separate substance—corticotropin—by Collip, Anderson and Thomson (37), Anselmino, Hoffman and Herold (38), Lyons (39) and Moon (40). At the moment we can exclude corticotropin or "adrenotropin" as a causative agent for the tabulated changes in blood sugar, though its presence does affect glycogen storage as noted below. We can also exclude such substances as intermedin, posterior lobe hormones, FSH, LH and thyrotropic hormone as the effective agents. Many of the effective preparations were first subjected to heat (boiling for 1 hour, or 60° C. for 5 hours).

Other data (Johnson and Riddle, unpublished) show that some of these same prolactin preparations also markedly increased the amount of histologically demonstrable *glycogen* in

TABLE I

Excerpt from data of Riddle and Dotti. Action of prolactin (3 tests of adrenotropin at bottom) on blood sugar in pigeons fasted 20–24 hours.

Preparation	Operative Procedures Used	Since Last Injection	No. Tested	Dosage		Glucose Found	
				Daily	Term	Control	Test
		hrs.		units prolac.	days	mgm.	mgm.
Prolactin, #380	Normals	24	8	30	1	192	241
" "	"	24	8	30	2	192	245
" "	"	24	8	30	3	192	256
Prolactin, #495H	Hypct.-castrate	24	3	18	8	183	211
" "	Hypophysectomy	24	2	18	8	188	214
" "	Hypct.-castrate	24	1	18	8	178	225
" "	Thyroidectomy	24	3	18	8	197	226
" "	Partial thydct	24	2	18	8	189	212
" "	Hypophysectomy	25	3	18	4	187	207
" "	Hypophysectomy	24	2	30	7	178	219
" "	Partial adrect	18	7	30	4	194	208
" "	Pt. adrect.-castr	18	2	30	4	179	225
" "	Pt. adrect.-thydct	18	1	30	4	192	221
" "	Pt. adrect.-hypct	18	2	30	4	185	219
Adrenotropic* #505	Thyroidectomy	21	3	1 (10 mg.)	4	219	232
" "	Hypophysectomy	21	1	1 (10 mg.)	4	167	165
Prolactin, #394H	Hypophysectomy	21	3	24	4	178	214
Adrenotropic* # 576	Hyp.-pancreatectomy	4–27	2	10 (10 mg.)	1–2	229	281
Prolactin #394H	Hyp.-pancreatectomy	4–27	4	80	1–2	223	275

*As prepared by method of Lyons (39) and Moon (40) by Dr. R. W. Bates; 10 mgm. daily in all tests, and containing the amount of prolactin indicated.

For performing, and checking the completeness of the various operations on animals utilized here, we are indebted to Dr. J. P. Schooley of our laboratory.

the livers of normal and hypophysectomized birds. This response followed the use of prolactin preparations with which we could demonstrate no enlargement of the 21-day rat adrenal, though it was evidently more pronounced when preparations having capacity to enlarge such adrenals were used. This result, however, was not further increased by the use of all the hormones contained in a whole extract of the pituitary. It seems that both prolactin and adrenotropin share in one phase of carbohydrate mobilization and utilization; other available evidence (41) points to rapid enlargement of livers (also intestine and pancreas) as a true prolactin response.

Still other data (Johnson and Riddle, unpublished) clearly indicate that prolactin (adrenotropic?) also increases the *fat* content of these bird livers (which are simultaneously both enlarging and increasing their glycogen content). This increase of liver fat (in hypophysectomized pigeons) can apparently be somewhat emphasized by the adrenotropin element of whole pituitary extracts. Possibly bearing on this point is the observation that, in normal doves, the injection of *estrone* increases the amount of fat in the liver. This ovarian hormone had no apparent effect upon hepatic glycogen.

From the above one gets indications that responses traceable to the prolactin-adrenotropin complex—at one point (liver fat) associated with action of a secondary product of the FSH complex—may encompass or include responses attributed to such additional "entities" as diabetogenic, ketogenic, and fat metabolism (and pancreatropic?).

Further consideration of prolactin, or possibly of the prolactin-adrenotropin complex, will indicate that in pigeons it too is responsible for splanchnomegaly—hitherto considered an aspect of the growth response and ascribable to a "growth" hormone. The data of Table 2 show that body growth, with rapid and excessive increase of liver weight, is obtained in Carneau pigeons by the administration of relatively highly purified preparations of prolactin. At three weeks after hatching the rapidly growing young pigeon shows crop-gland stimulation from prolactin produced in its own pituitary; and at this stage it shows—in addition to an amazing rate of body growth—relative *overgrowth* in liver, intestines, and probably in the pancreas. When similar birds were somewhat older, and in growth stasis, the administration of prolactin was followed by a resumption of body growth and by overgrowth of liver and

TABLE II

Excerpt from data of Bates, Riddle, Lahr and Schooley (41). Aspects of splanchnomegaly associated with the phase of rapid growth (1.3 months) in uninjected young White Carneau Pigeons and in similar young (2.2 mo.) injected for four days with prolactin. The standard deviation of the mean is given with each averaged value.

Route of Injection	No. of Birds	Age	Daily Dose	Body Weight	Liver	Intestine		Thyroids	Crop-glands
						Length (Gizzard to Anus)	Empty Weight		
		mo.	mgm.	grams	grams	cm.	grams	mgm.	mgm.
	Uninjected; young gest (1.3 mo.) group in extremely rapid growth.								
	12	1.3	.....	298± 4.9	9.3±0.3	117.8±2.2	10.3±0.4	30.5±1.7	1670± 70
	15	1.5	.....	457±11.6	10.0±0.3	117.8±1.4	13.2±0.4	33.3±1.5	1490± 49
	36	1.5	.....	431± 5.4	9.8±0.3	115.9±1.7	10.5±0.2	32.4±1.0	1630± 53
	27	2.2	.....	461±10.7	10.7±0.4	110.8±2.0	12.0±0.3	41.1±3.1	1245± 33
	Injected with iso-soluble fraction No. 474=FSH+ thyrotropic.								
Two routes*.....	10	2.2	5	453–35[1]	8.4±0.6	102.3±3.4	.....	77.7±12.0	1150± 64
	Injected with iso-insoluble fraction No. 469=prolactin.								
Intravenous.....	10	2.2	1	498+15	10.7±0.5	113.1±3.4	.....	42.7±2.4	1610±113
Intramuscular.....	15	2.2	1	457+24	10.8±0.6	111.1±2.9	.....	40.6±1.8	2355±188
Intracutaneous.....	10	2.2	1	460+43	13.3"0.9	117.3±4.6	.....	40.5±1.8	3790±233
Subcutaneous.....	10	2.2	0.1	466+ 5	9.3±0.7	104.4±1.9	.....	33.1±2.0	1255± 59
"	15	2.2	1	459+47	12.6±0.6	125.4±4.1	15.3±0.8	37.4±2.5	3940±232
"	10	2.2	5	453+75	16.4±0.9	127.0±4.4	.....	42.0±3.6	5845±476

*Intramuscular (5) and subcutaneous (5).
[1]Gain or loss of weight is indicated for all injected birds.

intestines (still other data obtained with Drs. Schooley, Lahr and Bates show this for the pancreas, and show that these aspects of body growth and visceral overgrowth are likewise obtained in hypophysectomized pigeons). Administration of an isosoluble pituitary preparation, known to be rich in FSH and thyrotropic hormones and probably containing all anterior lobe hormones except prolactin, produced none of these effects.

Though the above-described splanchnomegaly has not been induced in the rat, by the same preparations of prolactin which

TABLE III

Excerpt from data of Riddle and Dotti. Effect of *cortin* (Kendall) on blood sugar of doves and pigeons fasted 20–24 hours.

Animal Used (Operations Indicated)	Since Last Injection	No. Tests	Dosage		Glucose of Blood per 100 cc.	
			Daily	Term	Control	Test
	hrs.		cc.	days	mg.	mg.
Normal doves	7	12	0.3*	3–9	205	244
Normal doves	6[1]	4	0.5*	1	208	226
Normal doves	6[1]	4	0.5*	1	208	205[2]
Hypct. pigeons	6[1]	7	1.0*	1	173	193
Hypct. pigeons	6[1]	7	1.0*	1	173	175[2]
Thydct. pigeons	23	2	0.5	3–10	210	203
Part. thydct. pigeons	23	4	0.5	3–10	203	203
Thydct. pigeons	7[1]	3	1.0[1]	4	207	255
Part. thydct. pigeons	7[1]	2	1.0[1]	4	196	236
Hypct. pigeons	23	2	0.5	3–8	205	201

*Dose divided (twice daily).
[1]Intraperitoneal injection.
[2]Cortin inactivated by heat (96° C., 2 hrs.) used here.

produce it in doves and pigeons, positive results are regularly obtained in these latter species. The allocation to prolactin (or to heated prolactin-adrenotropin preparations) of these aspects of growth and overgrowth in these species provides a basis for further doubt as to the separateness or singleness of a "growth" hormone in the pituitary.

Returning now to the rôle of the adrenal cortex in carbohydrate metabolism one first notes that Long and Lukens (see Long, 42) have shown that glycosuria is produced in cats and rats by the effective pituitary hormone (or hormones) in the absence of both the pancreas and the hypophysis, but not in the absence of the adrenals. They further found that samples of

TABLE IV

Excerpt from data of Riddle and Dotti. Effect of pituitary (top) and of sex hormones (below) on serum calcium.

Preparation of Hormone	Dosage		Animals Used		Serum Calcium (mgm. per 100 cc.)	
	Quantity Daily	Term	No.	Kind	Control	Test
	cc. or units	days			mg.	mg.
Whole A. P. extr. (all A. P. hormones)	0.3 cc.	3	6	♂ ♀ Hypct. juv. pigeons	9.8	11.1
Prolactin	15.0 d. u.	10	10	♂ ♀ Hypct. juv. pigeons	9.8	9.9
FSH (+LH?) Mare serum	0.4 cc.	9	13	♂ ♀ Hyp. adult pigeons	9.3	10.8
FSH (+LH?) Mare serum	1.0 cc.	6	2	♀ Partial. adrenalect., ad.	11.6	17.0
FSH+thyrotropic (from A. P.)	2 mg.	5	2	♀ Thyroidectomy, ad	10.2	20.2
Estrone	250 R. U.	6	7	♂ ♀ Normal juv. pigeons	10.1	19.3
"	200 R. U.	7	2	♂ Hypct. pigeons, ad	9.0	25.1
"	3000 R. U.	2	2	♀ Dogs	10.0	12.3
"	3000 R. U.	8	3	♀ Rabbits	12.6	13.1
Dihydroestrone	1000 R. U.	3	3	♀ Non-laying hens	12.3	22.1
"	200 R. U.	6	2	♂ Part. hypct. ad. pigeons	9.4	10.7
"	375 R. U.	7	3	♂ ♀ Castrate rats	10.1	10.9
Progesterone	1 Rb. U.	3	2	♂ Normal pigeon, ad	10.2	12.0
"	0.1 Rb. U.	10	2	♀ Normal rats	10.4	11.6
Testosterone	2.5 mgm.	7	2	♂ Hypct. pigeon, ad	9.0	8.6
"	2.0 mgm.	7	4	♂ ♀ Normal pigeons, ad	10.1	9.9
"	5.0 mgm.	3	3	♂ ♀ Rabbits	13.1	13.1
Androstendiol	3.5 C. U.	7	2	♂ ♀ Hypct. pigeons, ad	9.3	9.3

prolactin (probably with some adrenal-stimulating power) prepared in our laboratory and also adrenotropin (probably containing prolactin) prepared by Collip were both very effective in the production of glycosuria in animals with intact adrenals. Houssay and Leloir (43), however, do not regard the adrenals as necessary to this response in toads and dogs. Britton (44) has long maintained that cortin (adrenal cortical hormone) raises the blood sugar of the mammalian species studied by him. The data cited below support Britton's views and extend the observations to birds.

In Table 3 are given some data of Riddle and Dotti (36, and unpublished) showing that in doves and pigeons cortin increases the blood sugar during the first several hours after injection but that this effect disappears within less than 23 hours. Of course the pituitary hormone which stimulates the cortex would provide for a continuous secretion of cortin and thus for its continuity of action on the blood sugar. We are much indebted to Dr. E. C. Kendall, Mayo Clinic, for the cortin used in the tabulated tests. Cortin kindly supplied by Dr. David Klein, The Wilson Laboratories, and Dr. R. L. Zwemer, Columbia University, gave similar results.

These several items indicate that the diabetogenic response is, in part at least, mediated through other incretory glands, and that cortin possibly shares in this response. Cortin—as shown by the work of Hartman, of this University, and by others—contributes so much to the well-being of the organism that it is difficult to conceive its exclusion from the growth response, and particularly to that response in hypophysectomized animals. Again, Hitchcock and Grubbs (45) recently report that the administration of cortical extract to normal human beings tends to increase their muscular efficiency during light work; and this sparing of heat production may have significance in the growth process. Finally, it is not improbable that the adrenal cortex produces still other hormones than cortin, and that hitherto their effects may have helped to swell the number of products supposedly produced in the pituitary gland.

We conclude this discussion with a very brief consideration of a response obtained with an FSH component (of basophilic origin), and with the secondary products (sex hormones) of its action on the gonads. Originally this study was directed to an examination of the evidence for the production by the anterior pituitary of a special "parathyrotropic" hormone—a

hormone alleged to stimulate the parathyroid glands to an increased production of parathormone, which in turn is known to increase the blood calcium.

In this study (Riddle and Dotti, 46; and unpublished data) it was soon found that prolactin and cortin were without effect, but the injection (prolonged and adequate dosage) of the FSH component into suitable animals resulted in increased amounts of calcium in the blood serum. Whole pituitary extracts gave a like result. The serum from pregnant mares, with FSH as the sole probably active factor, is effective. Later it was found that the *female sex hormones* have this power, and that male sex hormones have little or no similar action. Typical results are given in Table 4. We are greatly indebted to Dr. Erwin Schwenk, of the Schering Corporation, for the sex hormones used in that study.

Though it is uncertain whether or to what extent the parathyroids share in the response (castration prevents it) to FSH it is evident that the calcium elevating property of the sex hormones is exercised in the absence of either hypophysis, gonads, thyroids, and probably the parathyroids. It is also evident that before one can accept "parathyrotropic" pituitary hormone as an entity these new facts concerning the rôle of FSH and sex hormone must be concurrently examined.

On this day of continuous flux—along with gratifying advance—in all that pertains to the hormones of the anterior pituitary one may be neither too positive nor profitably attempt to be encyclopedic. In the present effort we have ventured—and have exposed all flanks in stating a point of view which we hope may be of momentary service. A little, but much too little, of the documentation of new research has indicated a part of the basis for an opinion that few true anterior pituitary hormones exist; that a greater variety of unfinished pituitary products exist; that secondary products of pituitary hormone action in other glands may have been mistaken for primary pituitary products; and that the true anterior pituitary hormones perhaps arrange themselves in two groups.

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BOOK NOTICES

Electricity as a Career

A high-school boy discusses his future with his father. While they are agreed on an electrical career, the methods involved in acquiring the proper training for any branch of this wide field are unknown to both of them. They enlist the aid of leading men (superintendents, etc.) in various fields: electrical engineering, radio, telegraphy, telephony, etc., who take them through plants and laboratories, and tell them of the preparation required for the different positions and the advantages accruing therefrom (disadvantages do not seem to be mentioned). No definite conclusion is reached, but the material is presented in very interesting form. The book is concluded with a list of electrical schools and colleges, radio schools, and welding schools. It is surprising to note that M. I. T. is relegated to the last named category.—J. B. GREEN.

Electrical Occupations, by L. A. Klinefelter. New York, E. P. Dutton & Co., 1937.

Termites

The authors have put scientific fact in plain understandable language so that many who might not otherwise know the interesting facts concerning the life, habits, and behavior of the termites can read of them in this interesting presentation. Although supposedly a book for young people, it is well adapted to older people who will find it quite entertaining. The tropical jungle is used as a setting for the discussion of the nest with its galleries, the casts, the daily activities and social life, their fossil ancestors, mating and reproduction, their guests and enemies.—D. M. DELONG.

Termite City, by Alfred E. Emerson and Eleanor Fish. Foreword by William Beebe. 127 pp. New York, Rand McNally & Co., 1937. $1.50.

Mountain Geography

Whether you are interested in mountains as places for recreation and adventure, or as land forms that present a variety of problems concerning types, agricultural possibilities, land utilization, or social and political regimes, Dr. Peattie's book is sure to stimulate your thinking, and afford a guide to the apprehension and appreciation of the multitude of environmental factors that influence mountain geography. Here is a pioneer book written for American students giving a broad survey of the results of long continued studies of European mountains, with carefully selected bibliographical notes. As stated in the publisher's note, the author makes "no attempt to preach determinism," but hopes to revive the interest of geographers in "the importance of environment rather than to confine themselves to man's part in reforming the environment."

—E. N. TRANSEAU.

Mountain Geography, a Critique and Field Study, by Roderick Peattie. xiv+257 pp. Cambridge, Mass., Harvard University Press. $4.00.

Cicadellidae

A check list of the family Cicadellidae in North America has just been published in mimeographed form. It comprises 145 genera and more than 1800 species as mentioned in literature up to September, 1937, with distribution records and citations to the original descriptions. Included in the publication is an index to genera arranged phylogenetically.

The booklet is neatly mimeographed and well bound in a serviceable heavy paper cover.—R. H. DAVIDSON.

Check List of the Cicadellidae (Homoptera) of North America, by Dwight M. DeLong and John S. Caldwell. 95 pp. Published by the authors, 1937. Price, $1.25. Copies may be obtained by writing Irona S. Winterrowd, Dept. of Zoology and Entomology, Ohio State University.

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